(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 628 311 A1**

(12) **EUROPEAN PATENT APPLICATION published in accordance with Art. 158(3) EPC**

(21) Application number: **93914963.9**

(51) Int. Cl.5: **A61K 31/52**, C07D 473/06

(22) Date of filing: **07.07.93**

(86) International application number:
PCT/JP93/00931

(87) International publication number:
WO 94/01114 (20.01.94 94/03)

(30) Priority: **08.07.92 JP 181025/92**

(43) Date of publication of application:
14.12.94 Bulletin 94/50

(84) Designated Contracting States:
AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL PT SE

(71) Applicant: **KYOWA HAKKO KOGYO CO., LTD.**
Ohtemachi Bldg., 6-1
Ohtemachi I-chome
Chiyoda-ku
Tokyo 100 (JP)

(72) Inventor: **SUZUKI, Fumio**
18-4, Fujimidai
Mishima-shi,
Shizuoka 411 (JP)
Inventor: **SHIMADA, Junichi**
270-1, Fushimi,
Shimizu-cho
Sunto-gun,
Shizuoka 411 (JP)
Inventor: **ISHII, Akio**
1501-17, Shimotogari,
Nagaizumi-cho
Sunto-gun,
Shizuoka 411 (JP)
Inventor: **NAKAMURA, Joji**
260-1, Takehara
Nagaizumi-cho
Sunto-gun,
Shizuoka 411 (JP)
Inventor: **ICHIKAWA, Shunji**
825, Hita,
Kannami-cho
Tagata-gun,
Shizuoka 419-01 (JP)
Inventor: **KITAMURA, Shigeto**
1-3-7, Naruse
Machida-shi,
Tokyo 194 (JP)
Inventor: **KOIKE, Nobuaki**
1188, Shimotogari,
Nagaizumi-cho
Sunto-gun,
Shizuoka 411 (JP)

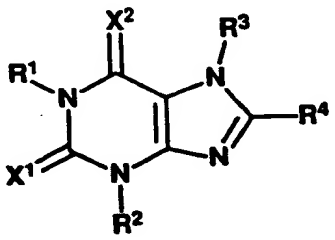
(74) Representative: **VOSSIUS & PARTNER**
Siebertstrasse 4
D-81675 München (DE)

(54) ANTIDEPRESSANT.

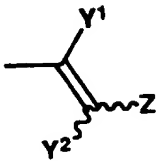
(57) An antidepressant containing an active ingredient comprising a xanthine derivative represented by general formule (I) or a pharmacologically acceptable salt thereof, wherein R^1, R^2 and R^3 may be the same or different from one another and each represents hydrogen, lower alkyl, alkyl or propargyl; R^4 represents cycloalkyl, $-(CH_2)_n-R^5$ (wherein R^5 represents optionally substituted aryl or optionally substituted heterocyclic group, and n represents an integer of 0 to 4) of group (A) wherein Y^1 and Y^2 may be the same or different from each other and each represents hydrogen, fluorine or methyl, and Z represents optionally substituted aryl, group (B)

EP 0 628 311 A1

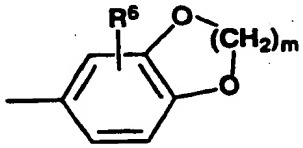
(wherein R^6 represents hydrogen, hydroxy, lower alkyl, lower alkoxy, halogen, nitro or amino, and m represents an integer of 1 to 3), or optionally substituted heterocyclic group; and X^1 and X^2 may be the same or different from each other and each represents O or S.



(I)



(A)

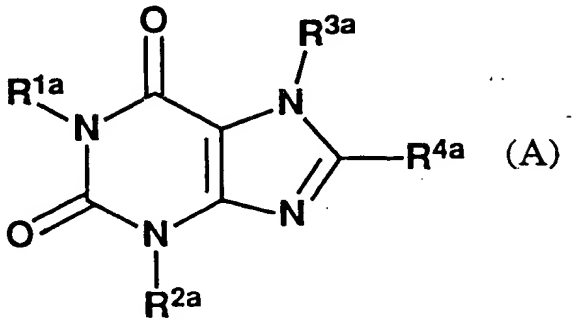


(B)

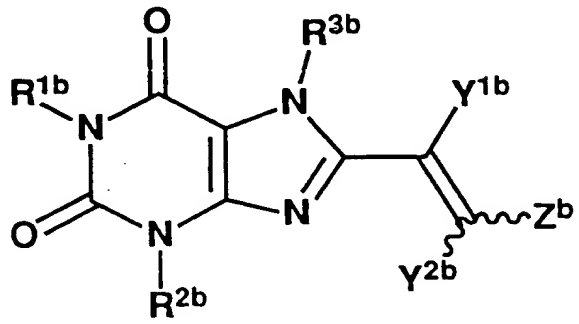
Technical Field

The present invention relates to an antidepressant containing a xanthine derivative or a pharmaceutically acceptable salt thereof as an active ingredient.

Background Art



(A)



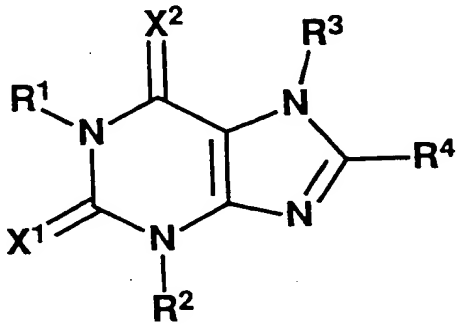
(B)

It is known that adenosine antagonistic action is found in compounds represented by Formula (A) in which R^{1a} and R^{2a} represent propyl, R^{3a} represents hydrogen, and R^{4a} represents substituted or unsubstituted phenyl, aromatic heterocyclic group, cycloalkyl, styryl, or phenylethyl [J. Med. Chem., 34, 1431 (1991)]. Further, Japanese Published Unexamined Patent Application No. 26516/72, as cerebral stimulants, compounds represented by Formula (B) in which R^{1b} and R^{2b} independently represent methyl or ethyl, R^{3b} represents methyl, Y^{1b} and Y^{2b} represent hydrogen, and Z^b represents phenyl or 3,4,5-trimethoxyphenyl. WO92/06976 discloses, as compounds having an adenosine A_2 receptor antagonistic activity and therapeutic effects on asthma and osteoporosis, compounds represented by Formula (B) in which R^{1b} and R^{2b} independently represent hydrogen, propyl, butyl, or allyl, R^{3b} represents hydrogen or lower alkyl, Y^{1b} and Y^{2b} independently represent hydrogen or methyl, and Z^b represents phenyl, pyridyl, imidazolyl, furyl, or thienyl unsubstituted or substituted by 1 to 3 substituents such as lower alkyl, hydroxy, lower alkoxy, halogen, amino, and nitro. Furthermore, other compounds represented by Formula (B) are known. One is 8-styryl caffeine which is a compound of Formula (B) in which R^{1b}, R^{2b}, and R^{3b} represent methyl, Y^{1b} and Y^{2b} represent hydrogen, and Z^b represents phenyl [Chem. Ber., 119, 1525 (1986)]. Another is a compound of Formula (B) in which R^{1b}, R^{2b}, and R^{3b} represent methyl, Y^{1b} and Y^{2b} represent hydrogen, and Z^b represents pyridyl, quinolyl, or methoxy-substituted or unsubstituted benzothiazolyl [Chem. Abst., 60, 1741h (1964)]. However, there is no description with regard to the pharmacologic action of any of these compounds.

It is clinically well known that the conventional antidepressant exhibits little effect in a single administration, and the effect is observed after at least about two weeks' consecutive administration. With the conventional antidepressant, the enhancement of clonidine-induced aggressive behavior in mice is observed after at least ten days' consecutive administration [J. Neural Transmission, 52, 189 (1981)].

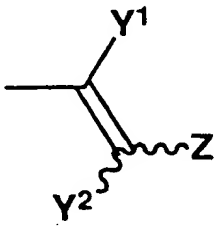
Disclosure of the Invention

The present invention relates to an antidepressant containing as an active ingredient a xanthine derivative or a pharmaceutically acceptable salt thereof, the xanthine derivative being represented by Formula (I):

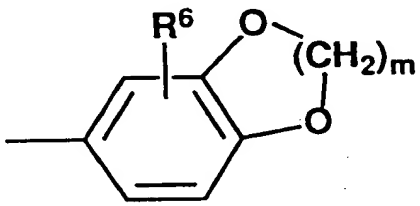


(I)

in which R^1, R^2, and R^3 represent independently hydrogen, lower alkyl, lower alkenyl, or lower alkynyl; R^4 represents cycloalkyl, $-(CH_2)_n-R^5$ (in which R^5 represents substituted or unsubstituted aryl or a substituted or unsubstituted heterocyclic group; and n is an integer of 0 to 4), or



(in which Y^1 and Y^2 represent independently hydrogen, halogen, or lower alkyl; and Z represents substituted or unsubstituted aryl,



(in which R^6 represents hydrogen, hydroxy, lower alkyl, lower alkoxy, halogen, nitro, or amino; and m represents an integer of 1 to 3), or a substituted or unsubstituted heterocyclic group);
and X^1 and X^2 represent independently O or S.

In the definitions of Compound (I), the lower alkyl means a straight-chain or branched alkyl group having 1 to 6 carbon atoms such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, neopentyl, and hexyl. The lower alkenyl means a straight-chain or branched alkenyl group having 2 to 6 carbon atoms such as vinyl, allyl, methacryl, crotyl, 3-butenyl, 2-pentenyl, 4-pentenyl, 2-hexenyl, 5-hexenyl. The lower alkynyl means a straight-chain or branched alkynyl group having 2 to 6 carbon atoms such as ethynyl, propargyl, 2-butynyl, 3-butynyl, 2-pentynyl, 4-pentynyl, 2-hexynyl, 5-hexynyl, 4-methyl-2-pentynyl. The aryl means phenyl or naphthyl. The cycloalkyl means a cycloalkyl group having 3 to 8 carbon atoms such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl. Examples of the heterocyclic group are furyl, thienyl, pyrrolyl, pyranyl, thiopyranyl, pyridyl, thiazolyl, imidazolyl, pyrimidyl, triazinyl, indolyl, quinolyl, purinyl, and benzothiazolyl. The halogen includes fluorine, chlorine,

bromine, and iodine.

The substituted aryl and the substituted heterocyclic ring each has 1 to 3 independently-selected substituents. Examples of the substituents are lower alkyl, hydroxy, substituted or unsubstituted lower alkoxy, halogen, nitro, amino, lower alkylamino, di(lower alkyl)amino, trifluoromethyl, trifluoromethoxy, benzyloxy, phenyl, and phenoxy. The lower alkyl and the alkyl moiety of the lower alkoxy, lower alkylamino, and di(lower alkyl)amino have the same meaning as the lower alkyl defined above. The halogen has the same meaning as defined above. Examples of the substituent of the substituted lower alkoxy are hydroxy, lower alkoxy, halogen, amino, azide, carboxy, and lower alkoxycarbonyl. The lower alkyl moiety of the lower alkoxy and lower alkoxycarbonyl has the same meaning as the lower alkyl defined above, and the halogen has the same meaning as defined above.

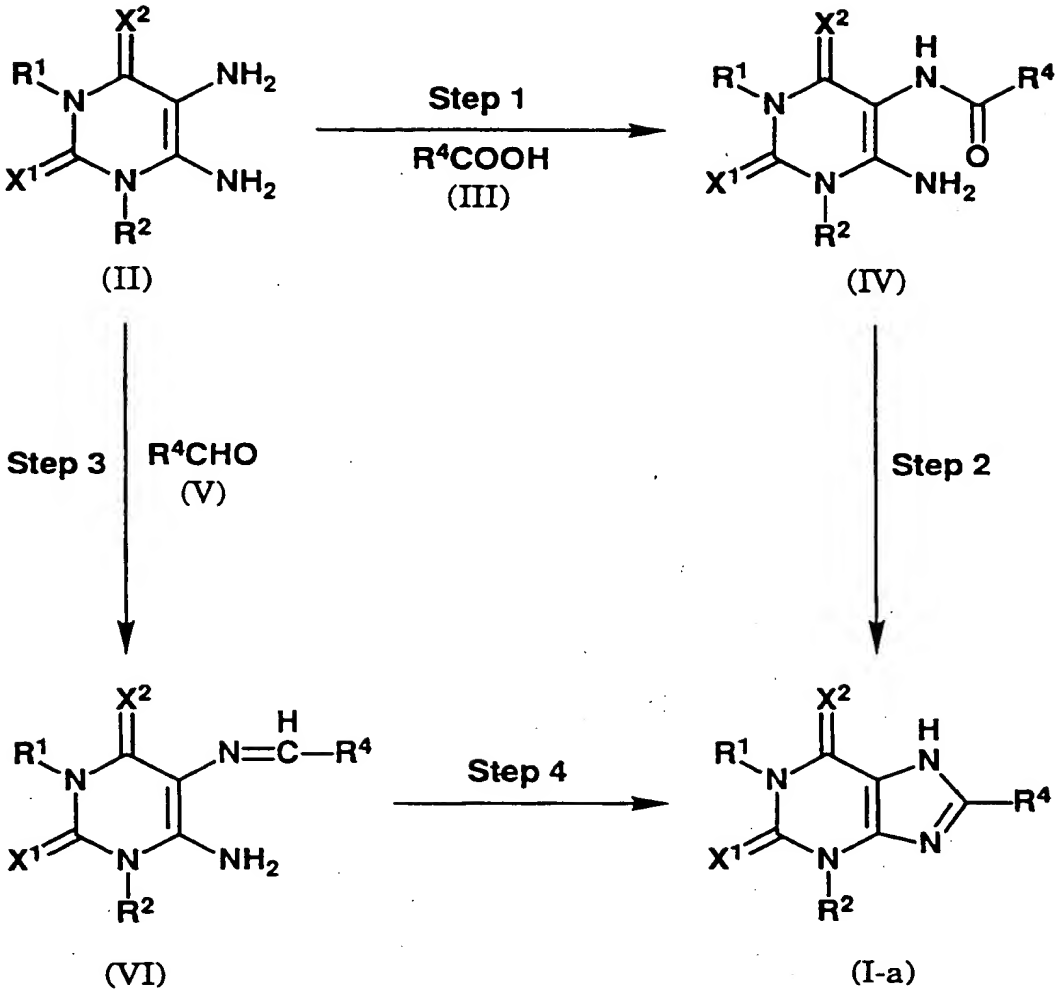
The pharmaceutically acceptable salts of Compounds (I) include pharmaceutically acceptable acid addition salts, metal salts, ammonium salts, organic amine addition salts, and amino acid addition salts.

Examples of the pharmaceutically acceptable acid addition salts are inorganic acid addition salts such as hydrochloride, sulfate, and phosphate, and organic acid addition salts such as acetate, maleate, fumarate, tartrate, and citrate. Examples of the pharmaceutically acceptable metal salts are alkali metal salts such as sodium salt and potassium salt, alkaline earth metal salts such as magnesium salt and calcium salt, aluminium salt, and zinc salt. Examples of the pharmaceutically acceptable ammonium salts are ammonium salt and tetramethyl ammonium salt. Examples of the pharmaceutically acceptable organic amine addition salts are salts with morpholine and piperidine. Examples of the pharmaceutically acceptable amino acid addition salts are salts with lysine, glycine, and phenylalanine.

The processes for producing Compounds (I) are described below. Compounds (I) can also be produced according to the methods described in, for example, Japanese Published Unexamined Patent Application No. 26516/72; J. Med. Chem., 34, 1431 (1991); Chem. Ber., 119, 1525 (1986); and Chem. Abst., 60, 1741h (1964).

Process 1

Compound (I-a) [Compound (I) in which R^3 is hydrogen] can be prepared by the following reaction steps:



(In the formulae, R^1, R^2, R^4, X^1, and X^2 have the same meanings as defined above.)

(STEP 1)

A uracil derivative (II) obtained by a known method [for example, Japanese Published Unexamined Patent Application No. 42383/84; J. Med. Chem., 32, 1873 (1989)] is allowed to react with either a carboxylic acid (III) or a reactive derivative thereof to give Compound (IV). Examples of the reactive derivative of the carboxylic acid (III) are acid halides such as acid chloride and acid bromide, active esters such as p-nitrophenyl ester and N-oxysuccinimide, commercially available acid anhydrides, acid anhydrides produced by using carbodiimides such as 3-(3-dimethylaminopropyl)-1-ethylcarbodiimide, diisopropyl carbodiimide, and dicyclohexyl carbodiimide, and mixed acid anhydrides with monoethyl carbonate or monoisobutyl carbonate. If the carboxylic acid (III) is used, the reaction is completed in 10 minutes to 5 hours at 50 to 200 °C without using a solvent.

If a reactive derivative of the carboxylic acid (III) is used, the reaction can be carried out according to a conventional method employed in peptide chemistry. That is, Compound (II) and a derivative of the carboxylic acid (III) are allowed to react, preferably in the presence of an additive or a base, to give Compound (IV). Examples of the solvent are halogenated hydrocarbons such as methylene chloride, chloroform, and ethylene dichloride, ethers such as dioxane and tetrahydrofuran, dimethylformamide, dimethylsulfoxide, and water if necessary. An example of the additive is 1-hydroxybenzotriazole. Examples of the base are pyridine, triethylamine, 4-dimethylaminopyridine, and N-methylmorpholine. The reaction is completed in 0.5 to 24 hours at -80 to 50 °C. The reactive derivative may be formed in the reaction system and then used without being isolated.

(STEP 2)

Compound (I-a) can be obtained by reaction of Compound (IV) carried out in any of the following manners: in the presence of a base (Method A); by treatment with a dehydrating agent (Method B); or by heating (Method C). In Method A, the reaction is carried out in a solvent in the presence of a base such as an alkali metal hydroxide (e.g. sodium hydroxide and potassium hydroxide). As the solvent, water, lower alcohols such as methanol and ethanol, ethers such as dioxane and tetrahydrofuran, dimethylformamide, dimethylsulfoxide, and the like may be used alone or in combination. The reaction is completed in 10 minutes to 6 hours at 0 to 180 °C.

In Method B, the reaction is carried out in an inert solvent or in the absence of a solvent using a dehydrating agent such as a thionyl halide (e.g. thionyl chloride) and a phosphorus oxyhalide (e.g. phosphorus oxychloride). Examples of the inert solvent are halogenated hydrocarbons such as methylene chloride, chloroform and ethylene dichloride, dimethylformamide, and dimethylsulfoxide. The reaction is completed in 0.5 to 12 hours at 0 to 180 °C.

In Method C, the reaction is carried out in a polar solvent such as dimethylformamide, dimethylsulfoxide, and Dowtherm A (Dow Chemicals). The reaction is completed in 10 minutes to 5 hours at 50 to 200 °C.

(STEP 3)

Compound (II) is allowed to react with an aldehyde (V) to give a Schiff's base (VI). As a reaction solvent, mixtures of acetic acid and a lower alcohol such as methanol and ethanol may be used. The reaction is completed in 0.5 to 12 hours at -20 to 100 °C.

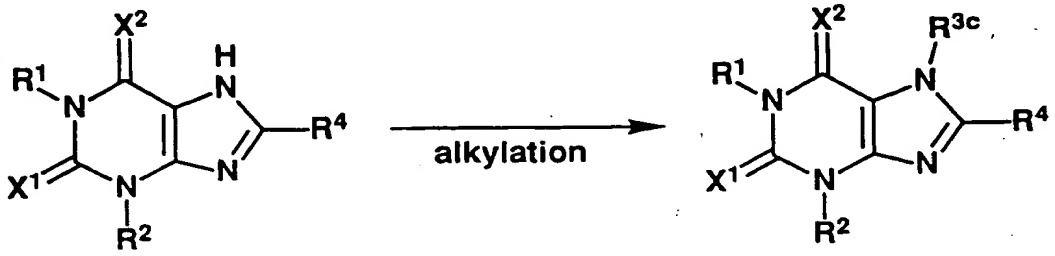
(STEP 4)

Compound (VI) is oxidatively cyclized in the presence of an oxidizing agent to form Compound (I-a). Examples of the oxidizing agent are oxygen, ferric chloride, cerium (IV) ammonium nitrate, and diethylazodicarboxylate. Examples of the solvent are lower alcohols such as methanol and ethanol, halogenated hydrocarbons such as methylene chloride and chloroform, and aromatic hydrocarbons such as toluene, xylene, and nitrobenzene. The reaction is completed in 10 minutes to 12 hours at 0 to 180 °C.

Process 2

Compound (I-b) [Compound (I) in which R^3 is a group other than hydrogen] can be prepared by the following reaction step.

Compound (I-b) is obtained from Compound (I-a) prepared by Process 1.



(I-a) (I-b)

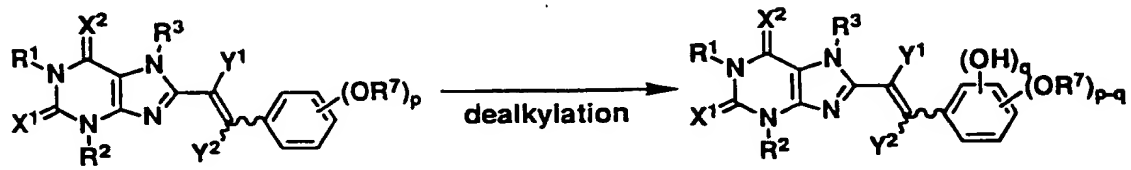
(In the formulae, R^{3c} represents a group other than hydrogen in the definition of R^3; and R^1, R^2, R^4, X^1, and X^2 have the same meanings as defined above.)

Compound (I-b) can be obtained by reaction of Compound (I-a) with an alkylating agent, in the presence of a base if necessary. Examples of the alkylating agent are alkyl halides such as methyl iodide and allyl bromide, dialkyl sulfates such as dimethyl sulfate, sulfonic esters such as allyl p-tolenesulfonate, and diazoalkanes such as diazomethane. Examples of the base are alkali metal carbonates such as sodium carbonate and potassium carbonate, alkali metal hydrides such as sodium hydride, and alkali metal alkoxides such as sodium methoxide and sodium ethoxide. As a reaction solvent, aromatic hydrocarbons such as toluene and xylene, ketones such as acetone and methyl ethyl ketone, dimethylformamide,

dimethylsulfoxide, or the like may be used. The reaction is completed in 0.5 to 24 hours at 0 to 180 °C.

Process 3

Compound (I-d) [Compound (I) in which Z is phenyl having hydroxy as substituent(s)] can be alternatively prepared by the following reaction step.



(I-c) (I-d)

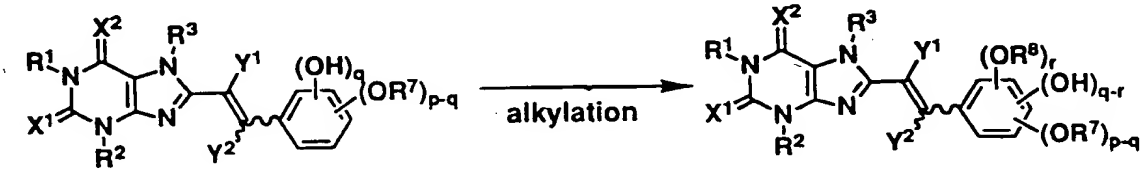
(In the formulae, R^7 represents substituted or unsubstituted lower alkyl; p and q are integers of 1 to 3 and $p \geq q$; and R^1, R^2, R^3, X^1, X^2, Y^1, and Y^2 have the same meanings as defined above.)

The substituted or unsubstituted lower alkyl in the definition of R^7 has the same meaning as defined above.

Compound (I-d) can be obtained by reaction of Compound (I-c) [Compound (I) in which Z is phenyl having lower alkoxy as substituent(s)] obtained by Process 1 or Process 2 with a dealkylating agent. Examples of the suitable dealkylating agent are boron tribromide and the complex thereof with dimethyl disulfide, boron trichloride, iodotrimethylsilane, sodium ethanethiolate, sodium benzenethiolate, and hydrobromic acid. A reaction solvent is selected from aromatic hydrocarbons such as toluene and xylene, halogenated hydrocarbons such as methylene chloride, chloroform, and ethylene dichloride, dimethylformamide, acetic acid, etc. depending upon the kind of the dealkylating agent used. The reaction is completed in 10 minutes to 120 hours at -30 to 140 °C.

Process 4

Compound (I-e) [Compound (I) in which Z is phenyl having lower alkoxy as substituent(s)] can be alternatively prepared by the following reaction step.



(I-d) (I-e)

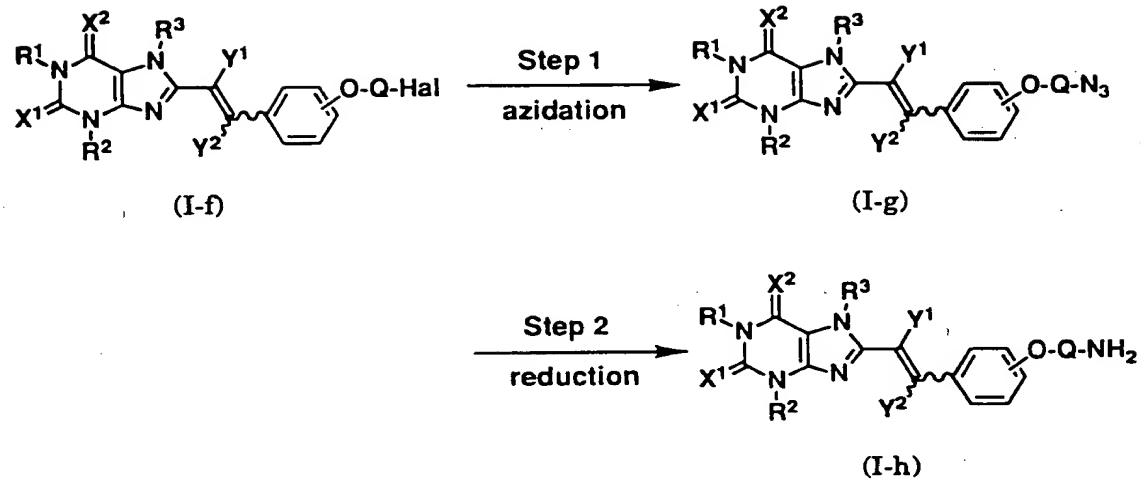
(In the formulae, R^8 represents substituted or unsubstituted lower alkyl; r is an integer of 1 to 3 and $q \geq r$; and R^1, R^2, R^3, R^7, X^1, X^2, Y^1, Y^2, p, and q have the same meanings as defined above.)

The substituted or unsubstituted lower alkyl in the definition of R^8 has the same meaning as defined above.

Compound (I-e) can be obtained from Compound (I-d) according to the method of Process 2.

Process 5

Compound (I-h) [Compound (I) in which Z is phenyl having amino-substituted lower alkoxy as the substituent] can be alternatively prepared by the following reaction step.



(I-f) (I-g) (I-h)

(In the formulae, Q represents lower alkylene; Hal represents chlorine, bromine, or iodine; and R^1, R^2, R^3, X^1, X^2, Y^1, and Y^2 have the same meanings as defined above.)

The lower alkylene in the definition of Q means a straight-chain or branched alkylene group having 1 to 6 carbon atoms such as methylene, ethylene, propylene, 1-methylethylene, butylene, 1-methylpropylene, 2-methylpropylene, pentylene, and hexylene.

(STEP 1)

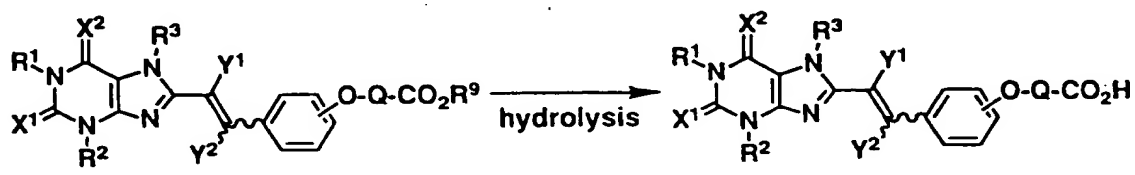
Compound (I-g) can be obtained by reaction of Compound (I-f) [Compound (I) in which Z is phenyl having chlorine, bromine, or iodine-substituted lower alkoxy as the substituent] obtained by Process 4 with 5 to 10 equivalents of sodium azide. As a reaction solvent, an inert solvent such as dimethylformamide may be used. The reaction is completed in 1 to 10 hours at 50 to 80 °C.

(STEP 2)

Compound (I-h) can be obtained by treatment of Compound (I-g) in an inert solvent such as tetrahydrofuran and dioxane in the presence of 2 to 5 equivalents of a reducing agent such as triphenylphosphine, followed by addition of an excess of water and further treatment for 1 to 10 hours at 50 °C to the boiling point of the solvent used.

Process 6

Compound (I-j) [Compound (I) in which Z is phenyl having carboxy-substituted lower alkoxy as the substituent] can be alternatively prepared by the following reaction step.



(I-i) (I-j)

(In the formulae, R^9 represents lower alkyl; and R^1, R^2, R^3, Q, X^1, X^2, Y^1, and Y^2 have the same meanings as defined above.)

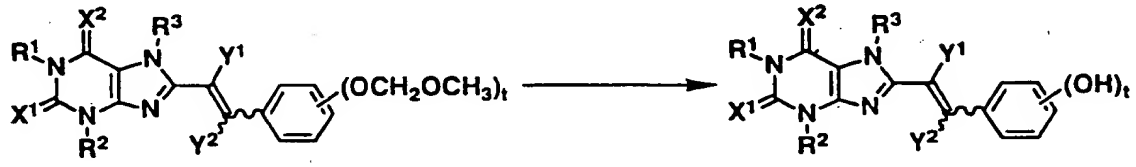
The lower alkyl in the definition of R^9 has the same meaning as defined above.

Compound (I-j) can be obtained by hydrolysis of Compound (I-i) [Compound (I) in which Z is phenyl having lower alkoxycarbonyl-substituted lower alkoxy as the substituent] obtained by Process 4 in the

presence of an alkali metal hydroxide such as sodium hydroxide and lithium hydroxide. As a reaction solvent, a mixture of water and an ether such as dioxane and tetrahydrofuran, or a mixture of water and an alcohol such as methanol and ethanol may be used. The reaction is completed in 10 minutes to 12 hours at room temperature to the boiling point of the solvent used.

Process 7

Compound (I-m) [Compound (I) in which Z is phenyl having hydroxy as the substituent(s)] can be alternatively prepared by the following reaction step.



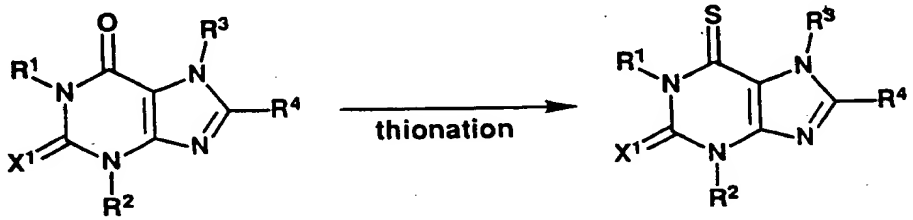
(I-k) (I-m)

(In the formulae, t is an integer of 1 to 3; and R^1, R^2, R^3, X^1, X^2, Y^1, and Y^2 have the same meanings as defined above.)

Compound (I-m) can be obtained by treatment of Compound (I-k) [Compound (I) in which Z is phenyl having methoxymethoxy as the substituent(s)] obtained by Process 1, Process 2, or Process 4 in the presence of hydrogen chloride gas, an aqueous solution of hydrochloric acid, or the like. As a reaction solvent, ethers such as dioxane and tetrahydrofuran, alcohols such as methanol and ethanol, or the like may be used. The reaction is completed in 1 to 20 hours at room temperature to the boiling point of the solvent used.

Process 8

Compound (I-o) [Compound (I) in which X^2 is S] can be alternatively prepared by the following reaction step.



(I-n) (I-o)

(In the formulae, R^1, R^2, R^3, R^4, and X^1 have the same meanings as defined above.)

Compound (I-o) can be obtained by reaction of Compound (I-n) [Compound (I) in which X^2 is O] obtained by Process 1 to Process 7 with a thionating agent. Examples of the thionating agent are phosphorus pentachloride and Leawsson's reagent. As a reaction solvent, pyridine, dimethylformamide, dioxane, tetrahydrofuran, or the like, preferably pyridine, may be used. The reaction is completed in 10 minutes to 36 hours at 50 to 180 °C.

The desired compounds in the processes described above can be isolated and purified by purification methods conventionally used in organic synthetic chemistry, for example, filtration, extraction, washing, drying, concentration, recrystallization, and various kinds of chromatography.

In the case where a salt of Compound (I) is desired and it is produced in the form of the desired salt, it can be subjected to purification as such. In the case where Compound (I) is produced in the free state and its salt is desired, Compound (I) is dissolved or suspended in a suitable solvent, followed by addition of an acid or a base to form a salt.

Compounds (I) and pharmaceutically acceptable salts thereof may be in the form of adducts with water or various solvents, which can also be used as the therapeutic agent of the present invention.

Examples of Compounds (I) are shown in Table 1, and the structures thereof are shown in Table 2.

Table 1-1

Compound No.	Name of the Compound
1	(E)-8-(3,4-dimethoxystyryl)-7-methyl-1,3-dipropyl-xanthine
2	(E)-8-(3,4,5-trimethoxystyryl)caffeine
3	(E)-7-methyl-1,3-dipropyl-8-styrylxanthine
4	(E)-1,3-diethyl-7-methyl-8-(3,4,5-trimethoxystyryl)xanthine
5	(E)-7-methyl-1,3-dipropyl-8-(3,4,5-trimethoxystyryl)xanthine
6	(E)-8-(4-methoxystyryl)-7-methyl-1,3-dipropyl-xanthine
7	(E)-1,3-diallyl-7-methyl-8-(3,4,5-trimethoxystyryl)xanthine
8	(E)-1,3-dibutyl-8-(3,4,5-trimethoxystyryl)xanthine
9	(E)-1,3-dibutyl-7-methyl-8-(3,4,5-trimethoxystyryl)xanthine
10	(E)-1,3-dipropyl-8-(3,4,5-trimethoxystyryl) xanthine
11	(E)-8-(3,4,5-trimethoxystyryl)theophylline
12	(E)-1,3-diallyl-8-(3,4,5-trimethoxystyryl) xanthine
13	(E)-8-(4-methoxy-2,3-dimethylstyryl)-1,3-dipropylxanthine
14	(E)-8-(4-methoxy-2,3-dimethylstyryl)-7-methyl-1,3-dipropylxanthine
15	(E)-8-(2,4-dimethoxy-3-methylstyryl)-1,3-dipropylxanthine
16	(E)-8-(2,4-dimethoxy-3-methylstyryl)-7-methyl-1,3-dipropylxanthine

Table 1-2

Compound No.	Name of the Compound
17	(E)-8-[2-(1,4-benzodioxan-6-yl)vinyl]-1,3-dipropylxanthine
18	(E)-8-[2-(1,4-benzodioxan-6-yl)vinyl]-7-methyl-1,3-dipropylxanthine
19	(E)-8-(3,4-methylenedioxystyryl)-1,3-dipropylxanthine
20	(E)-7-methyl-8-(3,4-methylenedioxystyryl)-1,3-dipropylxanthine
21	(E)-1,3-dipropyl-8-(2,3,4-trimethoxystyryl)-xanthine
22	(E)-7-methyl-1,3-dipropyl-8-(2,3,4-trimethoxystyryl)xanthine
23	(E)-1,3-dipropyl-8-(2,4,5-trimethoxystyryl)-xanthine
24	(E)-7-methyl-1,3-dipropyl-8-(2,4,5-trimethoxystyryl)xanthine
25	(E)-8-(2,4-dimethoxystyryl)-1,3-dipropylxanthine
26	(E)-8-(2,4-dimethoxystyryl)-7-methyl-1,3-dipropylxanthine
27	(E)-8-(4-benzyloxy-3,5-dimethoxystyryl)-1,3-dipropylxanthine
28	(E)-8-(4-benzyloxy-3,5-dimethoxystyryl)-7-methyl-1,3-dipropylxanthine
29	(E)-8-(2,3-dimethoxystyryl)-1,3-dipropylxanthine
30	(E)-8-(2,3-dimethoxystyryl)-7-methyl-1,3-dipropylxanthine
31	(E)-8-(3,4-dimethylstyryl)-1,3-dipropylxanthine
32	(E)-8-(3,4-dimethylstyryl)-7-methyl-1,3-dipropylxanthine

Table 1-3

Compound No.	Name of the Compound
33	(E)-8-(3,5-dimethoxystyryl)-1,3-dipropyl-xanthine
34	(E)-8-(3,5-dimethoxystyryl)-7-methyl-1,3-dipropylxanthine
35	(E)-8-(3-nitrostyryl)-1,3-dipropylxanthine
36	(E)-7-methyl-8-(3-nitrostyryl)-1,3-dipropyl-xanthine
37	(E)-8-(3-fluorostyryl)-1,3-dipropylxanthine
38	(E)-8-(3-fluorostyryl)-7-methyl-1,3-dipropyl-xanthine
39	(E)-8-(3-chlorostyryl)-1,3-dipropylxanthine
40	(E)-8-(3-chlorostyryl)-7-methyl-1,3-dipropyl-xanthine
41	(E)-8-(2-chlorostyryl)-1,3-dipropylxanthine
42	(E)-8-(2-chlorostyryl)-7-methyl-1,3-dipropyl-xanthine
43	(E)-8-(2-fluorostyryl)-1,3-dipropylxanthine
44	(E)-8-(2-fluorostyryl)-7-methyl-1,3-dipropyl-xanthine
45	(E)-8-(4-methoxy-2,5-dimethylstyryl)-1,3-dipropylxanthine
46	(E)-8-(4-methoxy-2,5-dimethylstyryl)-7-methyl-1,3-dipropylxanthine
47	(Z)-8-(3,4-dimethoxystyryl)-7-methyl-1,3-dipropylxanthine
48	(E)-8-(4-ethoxystyryl)-1,3-dipropylxanthine

Table 1-4

Compound No.	Name of the Compound
49	(E)-8-(4-ethoxystyryl)-7-methyl-1,3-dipropyl-xanthine
50	(E)-8-(4-propoxystyryl)-1,3-dipropylxanthine
51	(E)-7-methyl-8-(4-propoxystyryl)-1,3-dipropyl-xanthine
52	(E)-8-(4-butoxystyryl)-1,3-dipropylxanthine
53	(E)-8-(4-butoxystyryl)-7-methyl-1,3-dipropyl-xanthine
54	(E)-8-(3,4-dihydroxystyryl)-7-methyl-1,3-dipropylxanthine
55	(E)-8-(3,4-diethoxystyryl)-7-methyl-1,3-dipropylxanthine
56	(E)-8-(3-bromo-4-methoxystyryl)-1,3-dipropyl-xanthine
57	(E)-8-(3-bromo-4-methoxystyryl)-7-methyl-1,3-dipropylxanthine
58	(E)-8-(2-bromo-4,5-dimethoxystyryl)-1,3-dipropyl-xanthine
59	(E)-8-(2-bromo-4,5-dimethoxystyryl)-7-methyl-1,3-dipropylxanthine
60	(E)-8-(3-bromo-4,5-dimethoxystyryl)-1,3-dipropyl-xanthine
61	(E)-8-(3-bromo-4,5-dimethoxystyryl)-7-methyl-1,3-dipropylxanthine
62	(E)-8-[2-(4-methoxynaphthyl)vinyl]-1,3-dipropyl-xanthine
63	(E)-8-[2-(4-methoxynaphthyl)vinyl]-7-methyl-1,3-dipropylxanthine
64	(E)-8-(3-hydroxy-4-methoxystyryl)-7-methyl-1,3-dipropylxanthine

Table 1-5

Compound No.	Name of the Compound
65	(Z)-8-(3,4-dimethoxystyryl)-7-methyl-1,3-dipropyl-xanthine
66	(E)-8-(3,4-dimethoxystyryl)-7-ethyl-1,3-dipropyl-xanthine
67	(E)-8-(3,4-dimethoxystyryl)-7-propargyl-1,3-dipropylxanthine
68	(E)-8-[3,4-bis(methoxymethoxy)styryl]-7-methyl-1,3-dipropylxanthine
69	(E)-1,3-diallyl-8-(3,4-dimethoxystyryl)xanthine
70	(E)-1,3-diallyl-8-(3,4-dimethoxystyryl)-7-methyl-xanthine
71	(E)-8-(3,4-dimethoxystyryl)-1,3-dipropyl-2-thioxanthine
72	(E)-8-(3,4-dimethoxystyryl)-7-methyl-1,3-dipropyl-2-thioxanthine
73	(E)-8-(3,4-dimethoxystyryl)-1,3-diethylxanthine
74	(E)-8-(3,4-dimethoxystyryl)-1,3-diethyl-7-methyl-xanthine
75	(E)-8-(2,3-dimethoxystyryl)-1,3-diethylxanthine
76	(E)-8-(2,3-dimethoxystyryl)-1,3-diethyl-7-methyl-xanthine
77	(E)-8-(2,4-dimethoxystyryl)-1,3-diethylxanthine
78	(E)-8-(2,4-dimethoxystyryl)-1,3-diethyl-7-methyl-xanthine
79	(E)-1,3-diethyl-8-(2,3,4-trimethoxystyryl)-xanthine
80	(E)-1,3-diethyl-7-methyl-8-(2,3,4-trimethoxy-styryl)xanthine

Table 1-6

Compound No.	Name of the Compound
81	(E)-1,3-diethyl-8-(4-methoxy-2,3-dimethylstyryl)-xanthine
82	(E)-1,3-diethyl-8-(4-methoxy-2,3-dimethylstyryl)-7-methylxanthine
83	(E)-1,3-diethyl-8-(4-methoxy-2,5-dimethylstyryl)-xanthine
84	(E)-1,3-diethyl-8-(4-methoxy-2,5-dimethylstyryl)-7-methylxanthine
85	(E)-8-(2,4-dimethoxy-3-methylstyryl)-1,3-diethyl-xanthine
86	(E)-8-(2,4-dimethoxy-3-methylstyryl)-1,3-diethyl-7-methylxanthine
87	(E)-1,3-diethyl-8-(3,4-methylenedioxystyryl)-xanthine
88	(E)-1,3-diethyl-7-methyl-8-(3,4-methylenedioxy-styryl)xanthine
89	(E)-8-[2-(1,4-benzodioxan-6-yl)vinyl]-1,3-diethyl-xanthine
90	(E)-8-[2-(1,4-benzodioxan-6-yl)vinyl]-1,3-diethyl-7-methylxanthine
91	(E)-8-(2,3,4-trimethoxystyryl)theophylline
92	(E)-8-(2,3,4-trimethoxystyryl)caffeine
93	(E)-8-(4-methoxy-2,3-dimethylstyryl)theophylline
94	(E)-8-(4-methoxy-2,3-dimethylstyryl)caffeine
95	(E)-8-(3,4-methylenedioxystyryl)theophylline
96	(E)-8-(3,4-methylenedioxystyryl)caffeine

Table 1-7

Compound No.	Name of the Compound
97	(E)-8-(2,3-dimethoxystyryl)theophylline
98	(E)-8-(2,3-dimethoxystyryl)caffeine
99	(E)-8-(2,4-dimethoxystyryl)theophylline
100	(E)-8-(2,4-dimethoxystyryl)caffeine
101	(E)-8-(4-methoxy-2,5-dimethylstyryl)theophylline
102	(E)-8-(4-methoxy-2,5-dimethylstyryl)caffeine
103	(E)-8-(2,4-dimethoxy-3-methylstyryl)theophylline
104	(E)-8-(2,4-dimethoxy-3-methylstyryl)caffeine
105	(E)-8-(2-chloro-3,4-dimethoxystyryl)-1,3-diethylxanthine
106	(E)-8-(2-chloro-3,4-dimethoxystyryl)-1,3-diethyl-7-methylxanthine
107	(E)-8-(2-chloro-3,4-dimethoxystyryl)theophylline
108	(E)-8-(2-chloro-3,4-dimethoxystyryl)caffeine
109	(E)-8-(2,5-dimethylstyryl)-1,3-diethylxanthine
110	(E)-8-(2,5-dimethylstyryl)-1,3-diethyl-7-methylxanthine
111	(E)-8-(3,4-difluorostyryl)-1,3-diethylxanthine
112	(E)-8-(3,4-difluorostyryl)-1,3-diethyl-7-methylxanthine

Table 1-8

Compound No.	Name of the Compound
113	(E)-8-(3-bromo-4-methoxystyryl)-1,3-diethylxanthine
114	(E)-8-(3-bromo-4-methoxystyryl)-1,3-diethyl-7-methylxanthine
115	(E)-8-(3-bromo-4-methoxystyryl)theophylline
116	(E)-8-(3-bromo-4-methoxystyryl)caffeine
117	(E)-8-(2-bromo-4,5-dimethoxystyryl)-1,3-diethylxanthine
118	(E)-8-(2-bromo-4,5-dimethoxystyryl)-1,3-diethyl-7-methylxanthine
119	(E)-8-(4,5-dimethoxy-2-nitrostyryl)-1,3-diethylxanthine
120	(E)-8-(4,5-dimethoxy-2-nitrostyryl)-1,3-diethyl-7-methylxanthine
121	(E)-1,3-diethyl-8-(3-methoxy-2-nitrostyryl)xanthine
122	(E)-1,3-diethyl-8-(3-methoxy-2-nitrostyryl)-7-methylxanthine
123	(E)-8-(4-ethoxystyryl)-1,3-diethylxanthine
124	(E)-8-(4-ethoxystyryl)-1,3-diethyl-7-methylxanthine
125	(E)-1,3-diethyl-8-(4-propoxystyryl)xanthine
126	(E)-1,3-diethyl-7-methyl-8-(4-propoxystyryl)xanthine
127	(E)-1,3-diethyl-8-(3-fluorostyryl)xanthine
128	(E)-1,3-diethyl-8-(3-fluorostyryl)-7-methylxanthine

Table 1-9

Compound No.	Name of the Compound
129	(E)-8-(3,5-dimethoxystyryl)-1,3-diethylxanthine
130	(E)-8-(3,5-dimethoxystyryl)-1,3-diethyl-7-methylxanthine
131	(E)-8-(3-chlorostyryl)-1,3-diethylxanthine
132	(E)-8-(3-chlorostyryl)-1,3-diethyl-7-methylxanthine
133	(E)-1,3-diethyl-8-(α-methylstyryl)xanthine
134	(E)-1,3-diethyl-7-methyl-8-(α-methylstyryl)xanthine
135	(E)-1,3-diethyl-8-(4-trifluoromethylstyryl)xanthine
136	(E)-1,3-diethyl-7-methyl-8-(4-trifluoromethylstyryl)xanthine
137	(E)-1,3-diethyl-8-(α-fluorostyryl)xanthine
138	(E)-1,3-diethyl-8-(α-fluorostyryl)-7-methylxanthine
139	(E)-1,3-diethyl-8-(3-methoxystyryl)xanthine
140	(E)-1,3-diethyl-8-(3-methoxystyryl)-7-methylxanthine
141	(E)-8-(4-bromostyryl)-1,3-diethylxanthine
142	(E)-8-(4-bromostyryl)-1,3-diethyl-7-methylxanthine
143	(E)-1,3-diethyl-8-(3-trifluoromethoxystyryl)xanthine
144	(E)-1,3-diethyl-7-methyl-8-(3-trifluoromethoxystyryl)xanthine

Table 1-10

Compound No.	Name of the Compound
145	(E)-1,3-diethyl-8-(4-methoxymethoxystyryl)-xanthine
146	(E)-1,3-diethyl-8-(4-methoxymethoxystyryl)-7-methylxanthine
147	(E)-8-(4-butoxystyryl)-1,3-diethylxanthine
148	(E)-8-(4-butoxystyryl)-1,3-diethyl-7-methyl-xanthine
149	(E)-1,3-diethyl-8-(4-fluorostyryl)xanthine
150	(E)-1,3-diethyl-8-(4-fluorostyryl)-7-methyl-xanthine
151	(E)-1,3-diethyl-8-(4-methylstyryl)xanthine
152	(E)-1,3-diethyl-7-methyl-8-(4-methylstyryl)-xanthine
153	(E)-8-[3,5-bis(trifluoromethyl)styryl]-1,3-diethylxanthine
154	(E)-8-[3,5-bis(trifluoromethyl)styryl]-1,3-diethyl-7-methylxanthine
155	(E)-8-(3,5-difluorostyryl)-1,3-diethylxanthine
156	(E)-8-(3,5-difluorostyryl)-1,3-diethyl-7-methyl-xanthine
157	(E)-1,3-diethyl-8-(2-methoxystyryl)xanthine
158	(E)-1,3-diethyl-8-(2-methoxystyryl)-7-methyl-xanthine
159	(E)-1,3-diethyl-8-(3-nitrostyryl)xanthine
160	(E)-1,3-diethyl-7-methyl-8-(3-nitrostyryl)xanthine

Table 1-11

Compound No.	Name of the Compound
161	(E)-8-(3-bromostyryl)-1,3-diethylxanthine
162	(E)-8-(3-bromostyryl)-1,3-diethyl-7-methylxanthine
163	(E)-1,3-diethyl-8-(3-trifluoromethylstyryl)-xanthine
164	(E)-1,3-diethyl-7-methyl-8-(3-trifluoromethylstyryl)xanthine
165	(E)-8-(2-bromo-4,5-methylenedioxystyryl)-1,3-diethylxanthine
166	(E)-8-(2-bromo-4,5-methylenedioxystyryl)-1,3-diethyl-7-methylxanthine
167	(E)-1,3-diethyl-8-(2-fluorostyryl)xanthine
168	(E)-1,3-diethyl-8-(2-fluorostyryl)-7-methylxanthine
169	(E)-8-[4-(N,N-dimethylamino)styryl]-1,3-diethylxanthine
170	(E)-1,3-diethyl-8-(4-phenylstyryl)xanthine
171	(E)-1,3-diethyl-7-methyl-8-(4-phenylstyryl)-xanthine
172	(E)-1,3-diethyl-8-(3-fluoro-4-methoxystyryl)-xanthine
173	(E)-1,3-diethyl-8-(3-fluoro-4-methoxystyryl)-7-methylxanthine
174	(E)-1,3-diethyl-8-(4-methoxy-3-methylstyryl)-xanthine
175	(E)-1,3-diethyl-8-(4-methoxy-3-methylstyryl)-7-methylxanthine
176	(E)-8-(3-chloro-4-fluorostyryl)-1,3-diethylxanthine

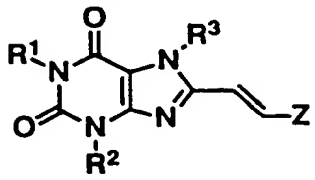
Table 1-12

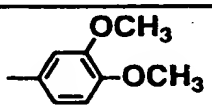
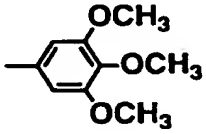
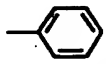
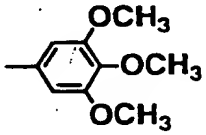
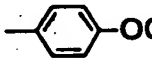
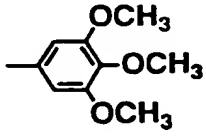
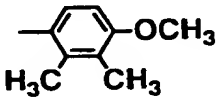
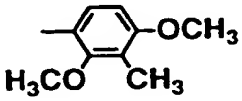
Compound No.	Name of the Compound
177	(E)-8-(3-chloro-4-fluorostyryl)-1,3-diethyl-7-methylxanthine
178	(E)-1,3-diethyl-8-(3-methoxy-4,5-methylenedioxystyryl)xanthine
179	(E)-1,3-diethyl-8-(3-methoxy-4,5-methylenedioxystyryl)-7-methylxanthine
180	(E)-1,3-diethyl-8-(3-fluoro-2-methylstyryl)-xanthine
181	(E)-1,3-diethyl-8-(3-fluoro-2-methylstyryl)-7-methylxanthine
182	(E)-8-(3,4-dihydroxystyryl)-1,3-diethyl-7-methylxanthine
183	(E)-1,3-diethyl-8-(3-hydroxy-4-methoxystyryl)-7-methylxanthine
184	(E)-1,3-diethyl-8-(4-hydroxystyryl)-7-methylxanthine
185	(E)-8-(4-benzyloxystyryl)-1,3-diethyl-7-methylxanthine
186	(E)-8-[4-(4-bromobutoxy)styryl]-1,3-diethyl-7-methylxanthine
187	(E)-8-[4-(4-azidobutoxy)styryl]-1,3-diethyl-7-methylxanthine
188	(E)-8-[4-(4-aminobutoxy)styryl]-1,3-diethyl-7-methylxanthine
189	(E)-8-(4-ethoxycarbonylmethoxystyryl)-1,3-diethyl-7-methylxanthine
190	(E)-8-(4-carboxymethoxystyryl)-1,3-diethyl-7-diethyl-7-methylxanthine
191	(E)-1,3-diethyl-8-(3-phenoxystyryl)xanthine
192	(E)-1,3-diethyl-7-methyl-8-(3-phenoxystyryl) xanthine

Table 1-13

Compound No.	Name of the Compound
193	(E)-1,3-diethyl-8-(4-hydroxystyryl)xanthine
194	(E)-1,3-diethyl-8-(4-hydroxy-2,3-dimethylstyryl)-7-methylxanthine

Table 2–1



Compd. No.	$-R^1$	$-R^2$	$-Z$	$-R^3$
1	$-(CH_2)_2CH_3$	$-(CH_2)_2CH_3$		$-CH_3$
2	$-CH_3$	$-CH_3$		"
3	$-(CH_2)_2CH_3$	$-(CH_2)_2CH_3$		"
4	$-CH_2CH_3$	$-CH_2CH_3$		"
5	$-(CH_2)_2CH_3$	$-(CH_2)_2CH_3$	"	"
6	"	"		"
7	$-CH_2-CH=CH_2$	$-CH_2-CH=CH_2$		"
8	$-(CH_2)_3CH_3$	$-(CH_2)_3CH_3$	"	$-H$
9	$-(CH_2)_3CH_3$	$-(CH_2)_3CH_3$	"	$-CH_3$
10	$-(CH_2)_2CH_3$	$-(CH_2)_2CH_3$	"	$-H$
11	$-CH_3$	$-CH_3$	"	"
12	$-CH_2-CH=CH_2$	$-CH_2-CH=CH_2$	"	"
13	$-(CH_2)_2CH_3$	$-(CH_2)_2CH_3$		"
14	"	"	"	$-CH_3$
15	"	"		$-H$
16	"	"	"	$-CH_3$

Tabl 2–2

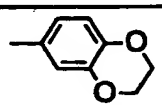
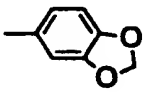
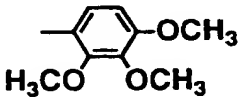
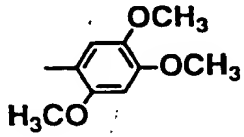
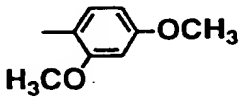
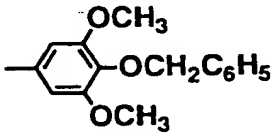
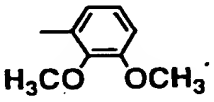
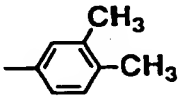
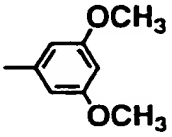
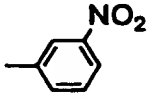
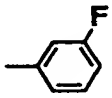
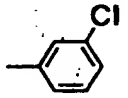
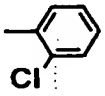
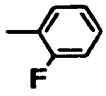
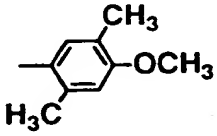
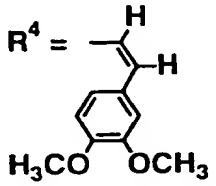
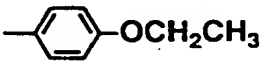
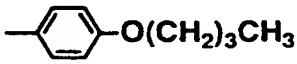
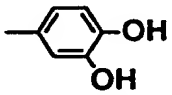
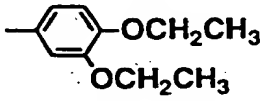
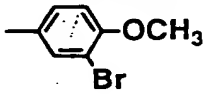
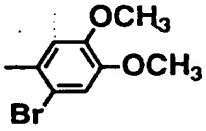
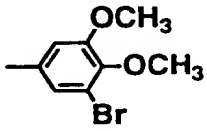
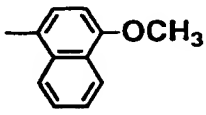
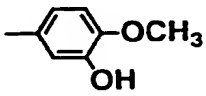
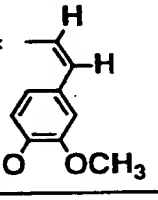
Compd. No.	$-R^1$	$-R^2$	$-Z$	$-R^3$
17	$-(CH_2)_2CH_3$	$-(CH_2)_2CH_3$		$-H$
18	"	"	"	$-CH_3$
19	"	"		$-H$
20	"	"	"	$-CH_3$
21	"	"		$-H$
22	"	"	"	$-CH_3$
23	"	"		$-H$
24	"	"	"	$-CH_3$
25	"	"		$-H$
26	"	"	"	$-CH_3$
27	"	"		$-H$
28	"	"	"	$-CH_3$
29	"	"		$-H$
30	"	"	"	$-CH_3$
31	"	"		$-H$
32	"	"	"	$-CH_3$

Table 2–3

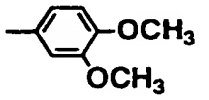
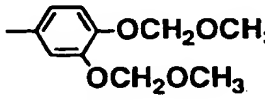
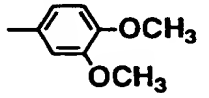
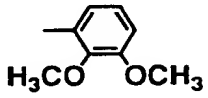
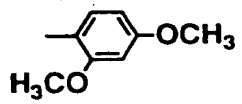
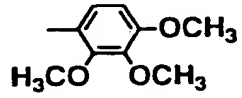
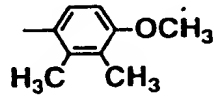
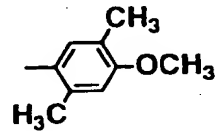
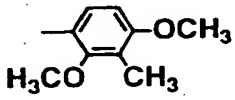
Compd. No.	$-R^1$	$-R^2$	$-Z$	$-R^3$
33	$-(CH_2)_2CH_3$	$-(CH_2)_2CH_3$		$-H$
34	"	"	"	$-CH_3$
35	"	"		$-H$
36	"	"	"	$-CH_3$
37	"	"		$-H$
38	"	"	"	$-CH_3$
39	"	"		$-H$
40	"	"	"	$-CH_3$
41	"	"		$-H$
42	"	"	"	$-CH_3$
43	"	"		$-H$
44	"	"	"	$-CH_3$
45	"	"		$-H$
46	"	"	"	$-CH_3$
47*	"	"		"

* : An about 6 : 4 mixture with Compound 1.

Table 2–4

Compd. No.	$-R^1$	$-R^2$	$-Z$	$-R^3$
48	$-(CH_2)_2CH_3$	$-(CH_2)_2CH_3$		$-H$
49	"	"	"	$-CH_3$
50	"	"		$-H$
51	"	"	"	$-CH_3$
52	"	"		$-H$
53	"	"	"	$-CH_3$
54	"	"		"
55	"	"		"
56	"	"		$-H$
57	"	"	"	$-CH_3$
58	"	"		$-H$
59	"	"	"	$-CH_3$
60	"	"		$-H$
61	"	"	"	$-CH_3$
62	"	"		$-H$
63	"	"	"	$-CH_3$
64	"	"		"
65	"	"	$R^4 =$ 	"

Tabl 2–5

Compd. No.	$-R^1$	$-R^2$	$-Z$	$-R^3$
66	$-(CH_2)_2CH_3$	$-(CH_2)_2CH_3$		$-C_2H_5$
67	"	"	"	$-CH_2C\equiv CH$
68	"	"		$-CH_3$
69	$-CH_2-CH=CH_2$	$-CH_2-CH=CH_2$		$-H$
70	"	"	"	$-CH_3$
71*	$-(CH_2)_2CH_3$	$-(CH_2)_2CH_3$	"	$-H$
72*	"	"	"	$-CH_3$
73	$-CH_2CH_3$	$-CH_2CH_3$	"	$-H$
74	"	"	"	$-CH_3$
75	"	"		$-H$
76	"	"	"	$-CH_3$
77	"	"		$-H$
78	"	"	"	$-CH_3$
79	"	"		$-H$
80	"	"	"	$-CH_3$
81	"	"		$-H$
82	"	"	"	$-CH_3$
83	"	"		$-H$
84	"	"	"	$-CH_3$
85	"	"		$-H$
86	"	"	"	$-CH_3$

* : 2–Thio form

Table 2–6

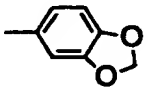
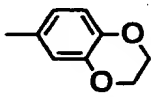
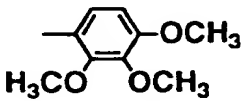
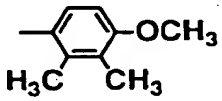
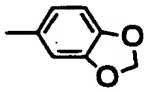
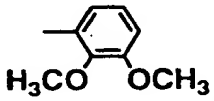
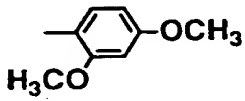
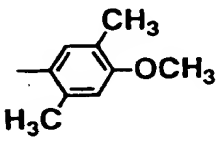
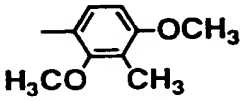
Compd. No.	$-R^1$	$-R^2$	$-Z$	$-R^3$
87	$-CH_2CH_3$	$-CH_2CH_3$		$-H$
88	"	"	"	$-CH_3$
89	"	"		$-H$
90	"	"	"	$-CH_3$
91	$-CH_3$	$-CH_3$		$-H$
92	"	"	"	$-CH_3$
93	"	"		$-H$
94	"	"	"	$-CH_3$
95	"	"		$-H$
96	"	"	"	$-CH_3$
97	"	"		$-H$
98	"	"	"	$-CH_3$
99	"	"		$-H$
100	"	"	"	$-CH_3$
101	"	"		$-H$
102	"	"	"	$-CH_3$
103	"	"		$-H$
104	"	"	"	$-CH_3$

Table 2–7

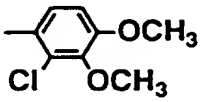
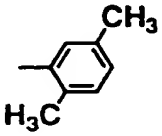
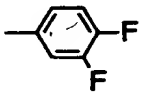
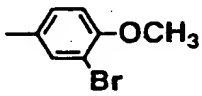
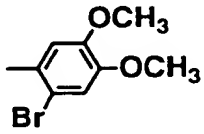
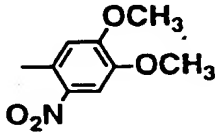
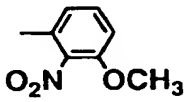
Compd. No.	$-R^1$	$-R^2$	$-Z$	$-R^3$
105	$-CH_2CH_3$	$-CH_2CH_3$		$-H$
106	"	"	"	$-CH_3$
107	$-CH_3$	$-CH_3$	"	$-H$
108	"	"	"	$-CH_3$
109	$-CH_2CH_3$	$-CH_2CH_3$		$-H$
110	"	"	"	$-CH_3$
111	"	"		$-H$
112	"	"	"	$-CH_3$
113	"	"		$-H$
114	"	"	"	$-CH_3$
115	$-CH_3$	$-CH_3$	"	$-H$
116	"	"	"	$-CH_3$
117	$-CH_2CH_3$	$-CH_2CH_3$		$-H$
118	"	"	"	$-CH_3$
119	"	"		$-H$
120	"	"	"	$-CH_3$
121	"	"		$-H$
122	"	"	"	$-CH_3$

Table 2–8

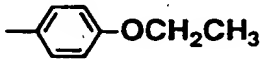
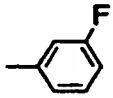
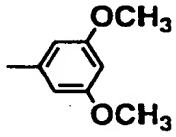
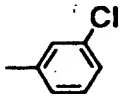
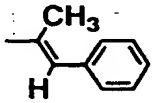
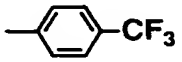
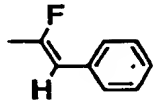
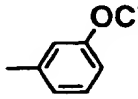
Compd. No.	$-R^1$	$-R^2$	$-Z$	$-R^3$
123	$-CH_2CH_3$	$-CH_2CH_3$		–H
124	"	"	"	$-CH_3$
125	"	"		–H
126	"	"	"	$-CH_3$
127	"	"		–H
128	"	"	"	$-CH_3$
129	"	"		–H
130	"	"	"	$-CH_3$
131	"	"		–H
132	"	"	"	$-CH_3$
133	"	"	R^4 = 	–H
134	"	"	"	$-CH_3$
135	"	"		–H
136	"	"	"	$-CH_3$
137	"	"	R^4 = 	–H
138	"	"	"	$-CH_3$
139	"	"		–H
140	"	"	"	$-CH_3$

Table 2–9

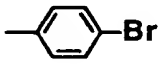
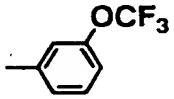
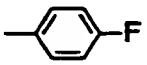
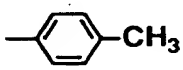
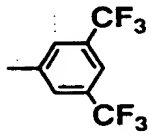
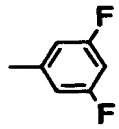
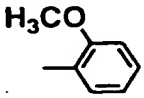
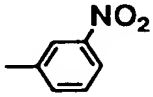
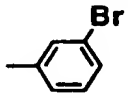
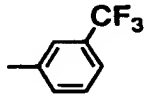
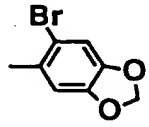
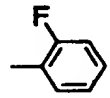
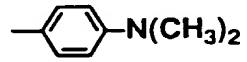
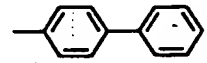
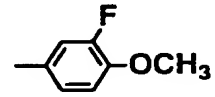
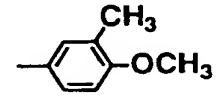
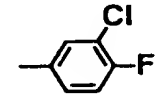
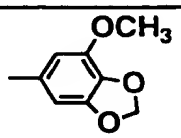
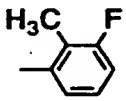
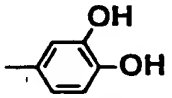
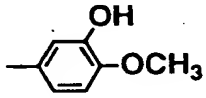
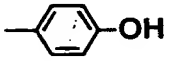
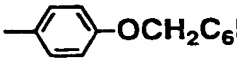
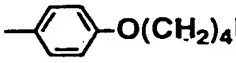
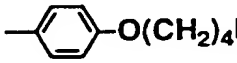
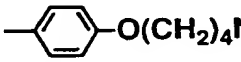
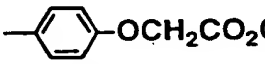
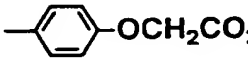
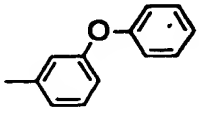
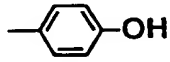
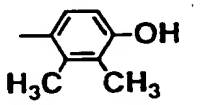
Compd. No.	$-R^1$	$-R^2$	$-Z$	$-R^3$
141	$-CH_2CH_3$	$-CH_2CH_3$		$-H$
142	"	"	"	$-CH_3$
143	"	"		$-H$
144	"	"	"	$-CH_3$
145	"	"		$-H$
146	"	"	"	$-CH_3$
147	"	"		$-H$
148	"	"	"	$-CH_3$
149	"	"		$-H$
150	"	"	"	$-CH_3$
151	"	"		$-H$
152	"	"	"	$-CH_3$
153	"	"		$-H$
154	"	"	"	$-CH_3$
155	"	"		$-H$
156	"	"	"	$-CH_3$
157	"	"		$-H$
158	"	"	"	$-CH_3$
159	"	"		$-H$
160	"	"	"	$-CH_3$

Table 2–10

Compd. No.	$-R^1$	$-R^2$	$-Z$	$-R^3$
161	$-CH_2CH_3$	$-CH_2CH_3$		$-H$
162	"	"	"	$-CH_3$
163	"	"		$-H$
164	"	"	"	$-CH_3$
165	"	"		$-H$
166	"	"	"	$-CH_3$
167	"	"		$-H$
168	"	"	"	$-CH_3$
169	"	"		$-H$
170	"	"		"
171	"	"	"	$-CH_3$
172	"	"		$-H$
173	"	"	"	$-CH_3$
174	"	"		$-H$
175	"	"	"	$-CH_3$
176	"	"		$-H$
177	"	"	"	$-CH_3$

Tabl 2–11

Compd. No.	$-R^1$	$-R^2$	$-Z$	$-R^3$
178	$-CH_2CH_3$	$-CH_2CH_3$		$-H$
179	"	"	"	$-CH_3$
180	"	"		$-H$
181	"	"	"	$-CH_3$
182	"	"		"
183	"	"		"
184	"	"		"
185	"	"		"
186	"	"		"
187	"	"		"
188	"	"		"
189	"	"		"
190	"	"		"
191	"	"		$-H$
192	"	"	"	$-CH_3$
193	"	"		$-H$
194	"	"		$-CH_3$

The pharmacological activities of Compounds (I) are shown below by test examples.

Test Example 1 Effect on Clonidine-Induced Aggressive Behavior

The effect of a test compound on the aggressive behavior induced by intraperitoneal administration of clonidine was investigated [Eur. J. Pharmacol., 29, 374 (1968)].

The experiment was performed by using several groups of male ddY mice (weighing 20 to 25 g, Japan SLC), each group consisting of two mice. The test compound was suspended in injectable distilled water (Otsuka Pharmaceutical Co., Ltd.). containing Tween 80 [polyoxyethylene (20) sorbitan monooleate]. Clonidine hydrochloride (Sigma Co.) was dissolved in physiological saline solution (Otsuka Pharmaceutical

Co., Ltd.). The test compound suspension and the control suspension were orally administered to separate groups of the mice (0.1 ml per 10 g of body weight). Sixty minutes after the oral administration of the test compound, clonidine hydrochloride (20 mg/kg) was intraperitoneally injected. The number of biting attacks during 30 minutes after clonidine treatment was counted. The effect of the compound was evaluated by comparing the average number of biting attacks of the test compound-administered groups with that of control groups (Statistical comparison : Student's t-test).

The results are shown in Table 3.

Table 3-1

Compd.	Dose (mg/kg, po)	Number of the Biting Attacks (mean ± S.E.M.)		Number of the Attacks of Test Compound-Treated Group/ Number of the Attacks of Control Group
		Control Group (number of animals)	Test Compound-Treated Group (number of animals)	
1	2.5	5.7 ± 1.52 (20)	27.5 ± 7.3* (15)	4.8
2	1.25	6.2 ± 1.87 (20)	29.0 ± 7.9* (15)	4.7
3	10	7.7 ± 2.39 (15)	26.1 ± 5.42** (15)	3.4
4	10	3.2 ± 1.24 (15)	51.3 ± 9.37*** (15)	16.0
4	2.5	6.8 ± 3.17 (15)	36.9 ± 7.81** (15)	5.4
4	0.63	2.6 ± 1.28 (10)	25.3 ± 4.51*** (15)	9.7
5	5	7.3 ± 2.56 (20)	25.4 ± 7.71* (15)	3.5
6	10	7.7 ± 2.39 (15)	83.7 ± 10.95** (15)	10.9
7	2.5	6.3 ± 3.06 (15)	40.1 ± 8.36** (15)	6.4
14	2.5	5.6 ± 3.06 (15)	40.7 ± 8.50* (15)	7.3
18	10	4.1 ± 1.80 (15)	26.2 ± 7.32** (15)	6.4
18	2.5	2.2 ± 1.25 (15)	8.6 ± 3.74* (15)	3.9

* : $p<0.05$; ** : $p<0.01$; *** : $p<0.001$

Table 3-2

Compd.	Dose (mg/kg, po)	Number of the Biting Attacks (mean ± S.E.M.)		Number of the Attacks of Test Compound-Treated Group/ Number of the Attacks of Control Group
		Control Group (number of animals)	Test Compound-Treated Group (number of animals)	
22	10	4.9 ± 2.41 (15)	33.1 ± 5.18*** (15)	6.8
49	10	2.6 ± 1.36 (10)	81.5 ± 13.97** (10)	31.3
70	10	7.6 ± 3.33 (10)	60.3 ± 11.71** (10)	7.9
74	10	4.3 ± 0.97 (15)	73.3 ± 8.75*** (15)	17.0
74	2.5	6.1 ± 1.71 (15)	51.3 ± 8.70*** (15)	8.4
74	0.63	6.1 ± 1.71 (15)	23.2 ± 5.19** (15)	3.8
78	10	5.3 ± 2.97 (15)	32.1 ± 7.31* (15)	6.1
80	10	4.9 ± 1.51 (15)	67.5 ± 9.35*** (15)	13.8
80	2.5	4.9 ± 1.51 (15)	59.3 ± 12.37*** (15)	12.1
80	0.63	6.5 ± 2.46 (15)	30.3 ± 7.00** (15)	4.7
82	10	7.7 ± 2.49 (15)	61.8 ± 11.89*** (15)	8.0
82	2.5	6.5 ± 2.46 (15)	59.0 ± 13.31*** (15)	9.1

* : $p<0.05$; ** : $p<0.01$; *** : $p<0.001$

Table 3–3

Compd.	Dose (mg/kg, po)	Number of the Biting Attacks (mean ± S.E.M.)		Number of the Attacks of Test Compound-Treated Group/ Number of the Attacks of Control Group
		Control Group (number of animals)	Test Compound-Treated Group (number of animals)	
82	0.63	6.5 ± 2.46 (15)	55.1 ± 12.58** (15)	8.5
84	10	2.9 ± 2.51 (15)	16.1 ± 3.70** (15)	6.9
86	10	5.0 ± 1.55 (15)	51.5 ± 8.73*** (15)	10.3
86	2.5	5.0 ± 1.55 (15)	30.9 ± 6.39** (15)	6.2
88	10	5.4 ± 2.03 (15)	40.9 ± 7.33*** (15)	7.6
88	2.5	5.4 ± 2.03 (15)	54.7 ± 10.76*** (15)	10.1
90	10	3.6 ± 1.14 (15)	18.7 ± 5.07* (15)	5.2
92	10	6.4 ± 2.98 (10)	55.4 ± 14.66** (10)	8.7
106	10	4.1 ± 2.60 (15)	22.3 ± 8.04* (15)	5.4
108	2.5	5.6 ± 2.54 (15)	25.6 ± 5.59** (15)	4.6
110	10	1.5 ± 0.74 (15)	42.5 ± 11.37** (15)	28.3
110	2.5	2.3 ± 0.92 (15)	36.6 ± 7.72*** (15)	27.9

* : $p<0.05$; ** : $p<0.01$; *** : $p<0.001$

Table 3-4

Compd.	Dose (mg/kg, po)	Number of the Biting Attacks (mean ± S.E.M.)		Number of the Attacks of Test Compound-Treated Group/ Number of the Attacks of Control Group
		Control Group (number of animals)	Test Compound-Treated Group (number of animals)	
114	10	2.1 ± 1.46 (15)	37.8 ± 8.66** (15)	18.0
124	10	3.7 ± 2.41 (10)	50.5 ± 17.7* (10)	13.6
124	2.5	2.5 ± 1.64 (15)	85.8 ± 12.41*** (15)	34.3
126	10	7.8 ± 2.6 (10)	80.0 ± 13.93*** (10)	10.3
130	10	10.8 ± 7.51 (10)	59.5 ± 13.61** (10)	5.5
136	10	2.6 ± 1.69 (10)	16.1 ± 5.26* (10)	6.2
140	10	10.8 ± 7.51 (10)	52.2 ± 11.79** (10)	4.8
146	10	2.9 ± 1.65 (10)	62.3 ± 14.16** (10)	21.5
148	10	2.9 ± 1.65 (10)	46.3 ± 9.40** (10)	16.0
150	10	2.9 ± 1.65 (10)	42.1 ± 10.18** (10)	14.5
152	10	12.4 ± 4.68 (5)	82.6 ± 23.07* (5)	6.7
162	10	2.1 ± 1.13 (15)	17.9 ± 6.67* (15)	8.5

* : $p<0.05$; ** : $p<0.01$; *** : $p<0.001$

Table 3-5

Compd.	Dose (mg/kg, po)	Number of the Biting Attacks (mean ± S.E.M.)		Number of the Attacks of Test Compound-Treated Group/ Number of the Attacks of Control Group
		Control Group (number of animals)	Test Compound-Treated Group (number of animals)	
168	10	7.6 ± 3.33 (10)	53.9 ± 8.59*** (10)	7.1
173	10	7.6 ± 3.33 (10)	46.8 ± 14.89* (10)	6.2
175	10	6.2 ± 3.02 (10)	49.1 ± 15.59* (10)	7.9
179	10	6.4 ± 2.98 (10)	67.7 ± 16.08** (10)	10.6
181	10	6.2 ± 3.02 (10)	49.5 ± 9.09*** (10)	8.0
184	10	7.6 ± 3.30 (10)	77.1 ± 11.47*** (10)	10.1
185	10	7.6 ± 3.30 (10)	46.9 ± 14.00* (10)	6.2
theo-phylline	10	3.6 ± 1.39 (15)	18.6 ± 3.58** (15)	5.2

* : $p<0.05$; ** : $p<0.01$; *** : $p<0.001$

As shown in Table 3, single administration of the compound according to the present invention enhanced the aggressive behavior induced by intraperitoneal administration of clonidine.

Test Example 2 Acute Toxicity Test

Test compounds were orally administered to groups of ddY-strain male mice weighing 20±1 g, each group consisting of three mice. Seven days after the administration, minimum lethal dose (MLD) of each compound was determined by observing the mortality.

The results are shown in Table 4.

Table 4-1

Compd. No.	MLD (mg/kg)	Compd. No.	MLD (mg/kg)
1	> 300	33	> 100
2	> 300	34	> 300
3	> 300	35	> 100
4	> 300	36	> 100
5	> 300	37	> 100
6	> 300	38	> 300
7	> 300	39	> 100
8	> 100	40	> 300
9	> 300	41	> 100
10	> 300	42	> 100
11	> 300	43	> 100
12	> 300	44	> 100
13	> 300	45	> 300
14	> 300	46	> 300
15	> 100	47	> 300
16	> 300	48	> 100
17	> 300	49	> 300
18	> 300	50	> 100
19	> 300	51	> 300
20	> 300	52	> 100
21	> 300	53	> 300
22	> 300	54	> 100
23	> 300	55	> 100
24	> 300	56	> 100
25	> 100	57	> 100
26	> 300	58	> 300
27	> 100	59	> 300
28	> 100	60	> 300
29	> 100	61	> 100
30	> 300	62	> 100
31	> 100	63	> 300
32	> 300	64	> 100

Table 4–2

Compd. No.	MLD (mg/kg)	Compd. No.	MLD (mg/kg)
65	> 300	97	> 100
66	> 300	98	> 300
67	> 300	99	> 100
68	> 100	100	> 300
69	> 100	101	> 100
70	> 100	102	> 100
71	> 100	103	> 100
72	> 300	104	> 100
73	> 300	105	> 100
74	> 300	106	> 300
75	> 300	107	> 100
76	> 300	108	> 300
77	> 100	109	> 300
78	> 300	110	> 300
79	> 300	111	> 300
80	> 300	112	> 300
81	> 300	113	> 100
82	> 300	114	> 100
83	> 300	115	> 100
84	> 300	116	> 300
85	> 300	117	> 100
86	> 300	118	> 100
87	> 300	119	> 100
88	> 300	120	> 300
89	> 100	121	> 300
90	> 300	122	> 100
91	> 300	123	> 100
92	> 300	124	> 300
93	> 100	125	> 100
94	> 100	126	> 300
95	> 300	127	> 100
96	> 300	128	> 300

Table 4-3

Compd. No.	MLD (mg/kg)	Compd. No.	MLD (mg/kg)
129	> 100	162	> 100
130	> 300	163	> 100
131	> 100	164	> 100
132	> 300	165	> 100
133	> 100	166	> 100
134	> 300	167	> 100
135	> 100	168	> 100
136	> 300	169	> 100
137	> 100	170	> 100
138	> 100	171	> 100
139	> 100	172	> 100
140	> 300	173	> 100
141	> 100	174	> 100
142	> 100	175	> 100
143	> 100	176	> 100
144	> 100	177	> 100
145	> 100	178	> 100
146	> 100	179	> 100
147	> 100	180	> 100
148	> 100	181	> 100
149	> 100	182	> 100
150	> 100	183	> 100
151	> 100	184	> 100
152	> 100	185	> 100
153	> 100	186	> 100
154	> 100	187	> 100
155	> 100	188	> 100
156	> 100	189	> 100
157	> 100	190	> 100
158	> 100	191	> 100
159	> 100	192	> 100
160	> 100	193	> 100
161	> 100	194	> 100

As shown in Table 4, the MLD value of all the compounds are greater than 100 mg/kg or 300 mg/kg, indicating that the toxicity of the compounds is weak. Therefore, these compounds can be safely used in a wide range of doses.

As described above, Compounds (I) and pharmaceutically acceptable salts thereof enhance clonidine-induced aggressive behavior. Thus, they are effective as antidepressants.

Compounds (I) and pharmaceutically acceptable salts thereof can be administered as they are, or in the form of various pharmaceutical compositions. The pharmaceutical compositions in accordance with the present invention can be prepared by uniformly mixing an effective amount of Compound (I) or a

pharmaceutically acceptable salt thereof, as an active ingredient, with a pharmaceutically acceptable carrier. It is desired that such pharmaceutical compositions are prepared in a unit dose form suitable for oral administration or administration through injection.

For preparing a pharmaceutical composition for oral administration, any useful pharmaceutically acceptable carrier can be used. For example, liquid preparations for oral administration such as suspension and syrup can be prepared using water, sugars such as sucrose, sorbitol, and fructose, glycols such as polyethylene glycol and propylene glycol, oils such as sesame oil, olive oil, and soybean oil, preservatives such as p-hydroxybenzoates, flavors such as strawberry flavor and peppermint, and the like. Powders, pills, capsules, and tablets can be prepared using excipients such as lactose, glucose, sucrose, and mannitol, disintegrating agents such as starch and sodium alginate, lubricants such as magnesium stearate and talc, binders such as polyvinyl alcohol, hydroxypropyl cellulose, and gelatin, surfactants such as fatty acid esters, plasticizers such as glycerin, and the like. Tablets and capsules are most useful oral unit dose forms because of the readiness of administration. For preparing tablets and capsules, solid pharmaceutical carriers are used.

Injectable preparations can be prepared using a carrier such as distilled water, a salt solution, a glucose solution, or a mixture of a salt solution and a glucose solution. The preparations can be prepared in the form of solution, suspension, or dispersion according to a conventional method by using a suitable solubilizing agent or suspending agent.

Compounds (I) and pharmaceutically acceptable salts thereof can be administered orally in the said dosage forms or parenterally as injections. The effective dose and the administration schedule vary depending upon the mode of administration, the age, body weight and conditions of a patient, etc. However, generally, Compound (I) or a pharmaceutically acceptable salt thereof is administered in a daily dose of 0.01 to 25 mg/kg in 3 to 4 parts.

Certain embodiments of the invention are illustrated in the following Examples and Reference Examples.

Best Mode For Carrying Out The Invention

Example 1 Tablets

Tablets having the following composition were prepared in a conventional manner.

Compound 1 (40 g) was mixed with 286.8 g of lactose and 60 g of potato starch, followed by addition of 120 g of a 10% aqueous solution of hydroxypropylcellulose. The resultant mixture was kneaded, granulated, and then dried by a conventional method. The granules were refined, thus obtaining granules used to make tablets. After mixing the granules with 1.2 g of magnesium stearate, the mixture was formed into tablets each containing 20 mg of the active ingredient by using a tablet maker (Model RT-15, Kikusui) having pestles of 8 mm diameter. The composition of each tablet thus prepared is shown in Table 5.

Table 5

Composition of One Tablet	
Compound 1	20 mg
Lactose	143.4mg
Potato Starch	30 mg
Hydroxypropylcellulose	6 mg
Magnesium Stearate	0.6mg
	200 mg

Example 2 Fine Granules

Fine granules having the following composition were prepared in a conventional manner.

Compound 74 (20 g) was mixed with 655 g of lactose and 285 g of corn starch, followed by addition of 400 g of a 10% aqueous solution of hydroxypropylcellulose. The resultant mixture was kneaded, granulated, and then dried by a conventional method, thus obtaining fine granules containing 20 g of the active ingredient in 1,000 g. The composition of one pack of the fine granules is shown in Table 6.

Table 6

Composition of One Pack of Fine Granules	
Compound 74	20 mg
Lactose	655 mg
Corn Starch	285 mg
Hydroxypropylcellulose	40 mg
	1,000 mg

Example 3 Capsules

Capsules having the following composition were prepared in a conventional manner.

Compound 80 (200 g) was mixed with 995 g of Avicel and 5 g of magnesium stearate. The mixture was put in hard capsules No. 4 each having a capacity of 120 mg by using a capsule filler (Model LZ-64, Zanashi), thus obtaining capsules each containing 20 mg of the active ingredient. The composition of one capsule thus prepared is shown in Table 7.

Table 7

Composition of One Capsule	
Compound 80	20 mg
Avicel	99.5mg
Magnesium Stearate	0.5mg
	120 mg

Example 4 Injections

Injections having the following composition were prepared in a conventional manner.

Compound 82 (1 g) was dissolved in 100 g of purified soybean oil, followed by addition of 12 g of purified egg yolk lecithin and 25 g of glycerine for injection. The resultant mixture was made up to 1,000 ml with distilled water for injection, thoroughly mixed, and emulsified by a conventional method. The resultant dispersion was subjected to aseptic filtration by using 0.2 μm disposable membrane filters, and then aseptically put into glass vials in 2 ml portions, thus obtaining injections containing 2 mg of the active ingredient per vial. The composition of one injection vial is shown in Table 8.

Table 8

Composition of One Injection Vial	
Compound 82	2 mg
Purified Soybean Oil	200 mg
Purified Egg Yolk Lecithin	24 mg
Glycerine for Injection	50 mg
Distilled Water for Injection	1.72 ml
	2.00 ml

Reference Example 1

(E)-8-(3,4-Dimethoxystyryl)-7-methyl-1,3-dipropylxanthine (Compound 1)

3,4-Dimethoxycinnamic acid (2.03 g, 9.74 mmol) and 3-(3-diethylaminopropyl)-1-ethylcarbodiimide hydrochloride (2.54 g, 13.3 mmol) were added to a mixture of water (60 ml) and dioxane (30 ml) containing 5,6-diamino-1,3-dipropyluracil (U.S. Patent No. 2,602,795) (2.00 g, 8.85 mmol). The resultant solution was stirred at room temperature for 2 hours at pH 5.5. After neutralization, the reaction solution was extracted three times with 50 ml of chloroform. The combined extract was washed with a saturated aqueous solution of sodium chloride and dried over anhydrous sodium sulfate, followed by evaporation under reduced pressure. The residue was purified by silica gel column chromatography (eluent: 2% methanol/chloroform) to give 3.47 g (yield 94%) of (E)-6-amino-5-(3,4-dimethoxycinnamoyl)amino-1,3-dipropyluracil (Compound A) as an amorphous substance.

NMR ($CDCl_3$; 90MHz) δ (ppm): 7.84(1H, brs), 7.50(1H, d, J = 15.9Hz), 7.10-6.65(3H, m), 6.53(1H, d, J = 15.9Hz), 5.75(2H, brs), 4.00-3.50(4H, m), 3.85(6H, brs), 2.00-1.40-(4H, m), 1.10-0.80(6H, m)

To 3.38 g (8.13 mmol) of Compound A were added 40 ml of dioxane and 80 ml of an aqueous 1N sodium hydroxide solution, followed by heating under reflux for 10 minutes. After cooling, the solution was neutralized, and deposited crystals were collected by filtration. Then, the collected crystals were recrystallized from dimethylsulfoxide/water to give 2.49 g (yield 77%) of (E)-8-(3,4-dimethoxystyryl)-1,3-dipropylxanthine(Compound B) as white crystals.

Melting Point: 260.0-263.8 °C

Elemental Analysis: $C_{21}H_{26}N_4O_4$			
Calcd. (%):	C, 63.30;	H, 6.57;	N, 14.06
Found (%):	C, 63.29;	H, 6.79;	N, 14.21

IR (KBr) ν_{max} (cm^{-1}): 1701, 1640

NMR (DMSO-d_6; 270MHz) δ (ppm): 13.39(1H, brs), 7.59 (1H, d, J = 16.7Hz), 7.26(1H, d, J = 1.8Hz), 7.13(1H, dd, J = 1.8, 8.6Hz), 6.98(1H, d, J = 8.6Hz), 6.95(1H, d, J = 16.7Hz), 3.99(2H, t), 4.00-3.85(2H, t), 3.83(3H, s), 3.80(3H, s), 1.80-1.55(4H, m), 1.00-0.85(6H, m)

Compound B (1.20 g, 3.02 mmol) was dissolved in 20 ml of dimethylformamide. To the solution were added 1.04 g (7.55 mmol) of potassium carbonate and subsequently 0.38 ml (6.04 mmol) of methyl iodide, and the resultant mixture was stirred at 50 °C for 30 minutes. After cooling, insoluble matters were filtered off, and 400 ml of water was added to the filtrate. The mixture was extracted three times with 100 ml of chloroform. The extract was washed twice with water and once with a saturated aqueous solution of sodium chloride, and dried over anhydrous sodium sulfate, followed by evaporation under reduced pressure. The residue was purified by silica gel column chromatography (eluent: 1% methanol/chloroform), followed by recrystallization from propanol/water to give 1.22 g (yield 98%) of Compound 1 as white needles.

Melting Point: 164.1-166.3 °C

Elemental Analysis: $C_{22}H_{28}N_4O_4$			
Calcd. (%):	C, 64.06;	H, 6.84;	N, 13.58
Found (%):	C, 64.06;	H, 6.82;	N, 13.80

IR (KBr) ν_{max} (cm^{-1}): 1692, 1657

NMR (DMSO-d_6; 270MHz) δ (ppm): 7.60(1H, d, J = 15.8Hz), 7.40(1H, d, J = 2.0Hz), 7.28(1H, dd, J = 2.0, 8.4Hz), 7.18(1H, d, J = 15.8Hz), 6.99(1H, d, J = 8.4Hz), 4.02(3H, s), 3.99(2H, t), 3.90-3.80(2H, m), 3.85(3H, s), 3.80(3H, s), 1.80-1.55(4H, m), 1.00-0.85(6H, m)

Reference Example 2

(E)-7-Methyl-1,3-dipropyl-8-styrylxanthine (Compound 3)

5,6-Diamino-1,3-dipropyluracil (U.S. Patent No. 2,602,795) (6.0 g, 26.5 mmol) was slowly added to a mixture of methanol (360 ml) and acetic acid (15 ml) containing cinnamaldehyde (3.34 ml, 26.5 mmol) under ice cooling. The resultant mixture was stirred at room temperature for 30 minutes, followed by evaporation under reduced pressure to give 6.30 g (yield 70%) of (E)-6-amino-5-(3-phenyl-3-propenylidene)-1,3-dipropyluracil (Compound C) as an amorphous substance.

Melting Point: 159.5-161.0 °C
IR (KBr) ν_{max} (cm^{-1}): 1687, 1593
NMR ($CDCl_3$; 90MHz) δ (ppm): 9.75-9.60(1H, m), 7.60-7.25(5H, m), 7.00-6.80(2H, m), 5.70(2H, brs), 4.00-3.70(4H, m), 2.00-1.40(4H, m), 1.10-0.75(6H, m)
MS m/e (relative intensity): 340(100, M^+), 130(86)

To 6.30 g (18.5 mmol) of Compound C was added 240 ml of ethanol, and the mixture was heated under reflux for 2 hours in the presence of 4.32 g (26.5 mmol) of ferric chloride. After cooling, deposited crystals were collected by filtration to give 3.61 g (yield 61%) of (E)-1,3-dipropyl-8-styrylxanthine(Compound D) as white crystals.

Melting Point: 259.3-261.0 °C (recrystallized from ethanol)

Elemental Analysis: $C_{19}H_{22}N_4O_2$			
Calcd. (%):	C, 67.43;	H, 6.55;	N, 16.56
Found (%):	C, 67.40;	H, 6.61;	N, 16.71

IR (KBr) ν_{max} (cm^{-1}): 1700, 1650, 1505
NMR (DMSO-d_6) δ (ppm): 13.59(1H, brs), 7.70-7.55 (3H, m), 7.50-7.30(3H, m), 7.06(1H, d, J = 16.5Hz), 3.99(2H, t), 3.86(2H, t), 2.80-2.50(4H, m), 0.95-0.80(6H, m)

Subsequently, the same procedure as in Reference Example 1 was repeated using Compound D in place of Compound B to give 1.75 g (yield 84%) of Compound 3 as white needles.

Melting Point: 162.8-163.2 °C

Elemental Analysis: $C_{20}H_{24}N_4O_2$			
Calcd. (%):	C, 68.16;	H, 6.86;	N, 15.90
Found (%):	C, 67.94;	H, 6.96;	N, 16.15

IR (KBr) ν_{max} (cm^{-1}): 1690, 1654, 1542, 1450, 1437
NMR ($CDCl_3$) δ (ppm): 7.79(1H, d, J = 15.8Hz), 7.65-7.55(2H, m), 7.48-7.35(3H, m), 6.92(1H, d, J = 15.8Hz), 4.11(2H, t), 4.06(3H, s), 3.98(2H, t), 2.00-1.60(4H, m), 1.08-0.95-(6H, m)

Reference Example 3

(E)-1,3-Dipropyl-8-(3,4,5-trimethoxystyryl)xanthine (Compound 9)

3,4,5-Trimethoxycinnamic acid (5.78 g, 24.3 mmol) and 6.36 g (33.2 mmol) of 3-(3-diethylaminopropyl)-1-ethylcarbodiimide hydrochloride were added to a mixture of dioxane (150 ml) and water (75 ml) containing 5.00 g (22.1 mmol) of 5,6-diamino-1,3-dipropyluracil. The resultant solution was stirred at room temperature at pH 5.5 for one hour. After the reaction, the solution was adjusted to pH 7 and extracted three times with chloroform. The combined extract was washed with a saturated aqueous solution of sodium chloride and dried over anhydrous sodium sulfate, followed by evaporation under reduced pressure. The residue was purified by silica gel column chromatography (eluent: 3% methanol/chloroform) to give 8.06 g (yield 82%) of (E)-6-amino-1,3-dipropyl-5-(3,4,5-trimethoxycinnamoylamino)uracil (Compound E) as an amorphous substance.

NMR ($CDCl_3$; 90MHz) δ (ppm): 7.85(1H, brs), 7.48(1H, d, J = 15.6Hz), 6.67(2H, s), 6.56(1H, d, J = 15.6Hz), 5.80(2H, brs), 4.00-3.70(4H, m), 3.89(9H, s), 1.80-1.45(4H,

m), 1.15-0.80(6H, m)

To 10.02 g (22.5 mmol) of Compound E were added 100 ml of dioxane and 100 ml of an aqueous 2N sodium hydroxide solution, and the solution was heated under reflux for 10 minutes. After cooling, the solution was neutralized, and deposited crystals were collected by filtration. Then, the collected crystals were recrystallized from dioxane/water to give 6.83 g (yield 91%) of Compound 9 as white crystals.

Melting Point: 161.8-162.6 °C

Elemental Analysis: $C_{22}H_{28}N_4O_5$			
Calcd. (%):	C, 61.66;	H, 6.58;	N, 13.07
Found (%):	C, 61.73;	H, 6.37;	N, 13.08

IR (KBr) ν_{max} (cm^{-1}): 1702, 1643

NMR ($CDCl_3$; 90MHz) δ (ppm): 12.87(1H, brs), 7.72(1H, d, J = 16.3Hz), 6.96(1H, d, J = 16.3Hz), 6.81-(2H, s), 4.30-3.95(4H, m), 3.92(6H, s), 3.90(3H, s), 2.10-1.50(4H, m), 1.02(2H, t), 0.90(2H, t)

Reference Example 4

(E)-7-Methyl-1,3-dipropyl-8-(3,4,5-trimethoxystyryl)xanthine (Compound 5)

The same procedure as in Reference Example 1 was repeated using Compound 9 in place of Compound B to give 1.75 g (yield 84%) of Compound 5 as white needles.

Melting Point: 168.4-169.1 °C (recrystallized from ethanol/water)

Elemental Analysis: $C_{23}H_{30}N_4O_5$			
Calcd. (%):	C, 62.42;	H, 6.83;	N, 12.66
Found (%):	C, 62.48;	H, 6.60;	N, 12.70

IR (KBr) ν_{max} (cm^{-1}): 1698, 1659

NMR ($CDCl_3$; 90MHz) δ (ppm): 7.71(1H, d, J = 15.8Hz), 6.86(2H, s), 6.78(1H, d, J = 15.8Hz), 4.30-3.95-(4H, m), 4.07(3H, s), 3.93(6H, s), 3.90(3H, s), 2.05-1.50(4H, m), 1.20-0.85(6H, m)

Reference Example 5

(E)-8-(4-Methoxystyryl)-7-methyl-1,3-dipropylxanthine (Compound 6)

Substantially the same procedure as in Reference Example 1 was repeated using 2.00 g (8.85 mmol) of 5,6-diamino-1,3-dipropyluracil and 1.73 g (9.74 mmol) of 4-methoxycinnamic acid to give 2.29 g (overall yield 68%) of Compound 6.

Melting Point: 159.8-161.3 °C (recrystallized from ethanol/water)

Elemental Analysis: $C_{21}H_{26}N_4O_3$			
Calcd. (%):	C, 65.94;	H, 6.85;	N, 14.64
Found (%):	C, 65.92;	H, 6.90;	N, 14.88

IR (KBr) ν_{max} (cm^{-1}): 1695, 1658

NMR (DMSO-d_6) δ (ppm): 7.72(2H, d, J = 8.8Hz), 7.61(1H, d, J = 15.8Hz), 7.16(1H, d, J = 15.8Hz), 4.05-3.95(2H, m), 4.00(3H, s), 3.83(2H, t), 3.80(3H, s), 1.85-1.50(4H, m), 1.00-0.85(6H, m)

Reference Example 6

(E)-1,3-Diallyl-8-(3,4,5-trimethoxystyryl)xanthine (Compound 11)

Substantially the same procedure as in Reference Example 3 was repeated using 3.0 g (13.5 mmol) of 1,3-diallyl-5,6-diaminouraciland 3.55 g (14.9 mmol) of 3,4,5-trimethoxycinnamic acid to give 4.48 g (yield 75%) of (E)-1,3-diallyl-6-amino-5-(3,4,5-trimethoxycinnamoylamino)uracil (Compound F) as an amorphous substance.

NMR ($CDCl_3$; 90MHz) δ (ppm): 7.90(1H, brs), 7.56(1H, d, J = 16.0Hz), 6.71(2H, s), 6.57(1H, d, J = 16.0Hz), 6.15-5.60(4H, m), 5.50-5.05(4H, m), 4.75-4.45(4H, m), 3.90(9H, s)

Substantially the same procedure as in Reference Example 3 was repeated using 4.34 g (9.82 mmol) of Compound F in place of Compound E to give 2.81 g (yield 68%) of Compound 11 as a pale yellowish green powder.

Melting Point: 253.1-255.4 °C (recrystallized from dioxane)

Elemental Analysis: $C_{22}H_{24}N_4O_5 \cdot 1/2H_2O$			
Calcd. (%):	C, 60.96;	H, 5.81;	N, 12.93
Found (%):	C, 61.05;	H, 5.60;	N, 12.91

IR (KBr) ν_{max} (cm^{-1}): 1704, 1645, 1583, 1510

NMR ($CDCl_3$) δ (ppm): 12.94(1H, brs), 7.73(1H, d, J = 16.3Hz), 7.05(1H, d, J = 16.3Hz), 6.81(2H, s), 6.12-5.92(2H, m), 5.37-5.22(4H, m), 4.83-4.76(4H, m), 3.91(6H, s), 3.90(3H, s)

Reference Example 7

(E)-1,3-Diallyl-7-methyl-8-(3,4,5-trimethoxystyryl)xanthine (Compound 7)

Substantially the same procedure as in Reference Example 1 was repeated using 1.13 g (2.67 mmol) of Compound 11 in place of Compound B to give 620 mg (yield 53%) of Compound 7 as pale yellow needles.

Melting Point: 189.0-191.1 °C (recrystallized from ethyl acetate)

Elemental Analysis: $C_{23}H_{26}N_4O_5$			
Calcd. (%):	C, 63.00;	H, 5.97;	N, 12.77
Found (%):	C, 63.00;	H, 6.05;	N, 12.85

IR (KBr) ν_{max} (cm^{-1}): 1699, 1660

NMR ($CDCl_3$; 90MHz) δ (ppm): 7.78(1H, d, J = 16.0Hz), 6.85(2H, s), 6.84(1H, d, J = 16.0Hz), 6.30-5.75-(2H, m), 5.45-5.10(4H, m), 4.85-4.55(4H, m), 4.07(3H, s), 3.92(6H, s), 3.90(3H, s)

Reference Example 8

(E)-1,3-Dibutyl-8-(3,4,5-trimethoxystyryl)xanthine (Compound 8)

Substantially the same procedure as in Reference Example 1 was repeated using 4.75 g (18.7 mmol) of 5,6-diamino-1,3-dibutyluracil and 4.90 g (20.6 mmol) of 3,4,5-trimethoxycinnamic acid to give 10.6 g of crude (E)-6-amino-1,3-dibutyl-5-(3,4,5-trimethoxycinnamoylamino)uracil (Compound G) as an amorphous substance.

NMR ($CDCl_3$; 90MHz) δ (ppm): 7.85(1H, brs), 7.53(1H, d, J = 16.0Hz), 6.72(2H, s), 6.57(1H, d, J = 16.0Hz), 5.74(2H, brs), 4.05-3.70(4H, m), 3.89(9H, s), 1.80-1.15(8H, m), 1.15-0.80(6H, m)

Substantially the same procedure as in Reference Example 1 was repeated using 10.6 g of Compound G in place of Compound A to give 5.80 g (overall yield 68%) of Compound 8 as a white powder.

Melting Point: 205.8-207.2 °C (recrystallized from ethyl acetate)

Elemental Analysis: $C_{24}H_{32}N_4O_5$			
Calcd. (%):	C, 63.14;	H, 7.06;	N, 12.27
Found (%):	C, 63.48;	H, 6.71;	N, 12.43

IR (KBr) ν_{max} (cm^{-1}): 1698, 1643, 1584, 1570, 1504
NMR ($CDCl_3$; 90MHz) δ (ppm): 7.75(1H, d, J = 15.8Hz), 6.98(1H, d, J = 15.8Hz), 6.82(2H, s), 4.30-4.12-(4H, m), 3.98(6H, s), 3.93(3H, s), 2.00-0.80(14H, m)

Reference Example 9

(E)-1,3-Dibutyl-7-methyl-8-(3,4,5-trimethoxystyryl)xanthine (Compound 9)

Substantially the same procedure as in Reference Example 1 was repeated using 2.50 g (5.48 mmol) of Compound 8 obtained in Reference Example 8 in place of Compound B to give 2.36 g (yield 92%) of Compound 9 as a pale green powder.
Melting Point: 136.8-137.3 °C (recrystallized from ethanol/water)

Elemental Analysis: $C_{25}H_{34}N_4O_5$			
Calcd. (%):	C, 63.81;	H, 7.28;	N, 11.91
Found (%):	C, 63.63;	H, 6.93;	N, 11.99

IR (KBr) ν_{max} (cm^{-1}): 1692, 1659
NMR ($CDCl_3$; 90MHz) δ (ppm): 7.68(1H, d, J = 15.8Hz), 6.80(2H, s), 6.79(1H, d, J = 15.8Hz), 4.30-3.90-(4H, m), 4.03(3H, s), 3.95(6H, s), 3.91(3H, s), 1.90-1.10(8H, m), 1.05-0.80(6H, m)

Reference Example 10

(E)-8-(4-Methoxy-2,3-dimethylstyryl)-1,3-dipropylxanthine (Compound 13)

Substantially the same procedure as in Reference Example 1 was repeated using 2.31 g (10.24 mmol) of 5,6-diamino-1,3-dipropyluracil and 2.42 g (15.4 mmol) of 4-methoxy-2,3-dimethylcinnamic acid. Then, the resultant crude crystals were recrystallized from dioxane/water to give 1.96 g (yield 48%) of Compound 13 as a white powder.
Melting Point: 270.7-271.3 °C

Elemental Analysis: $C_{22}H_{28}N_4O_3$			
Calcd. (%):	C, 66.64;	H, 7.11;	N, 14.13
Found (%):	C, 66.68;	H, 7.20;	N, 14.04

IR (KBr) ν_{max} (cm^{-1}): 1704, 1650, 1591, 1269
NMR (DMSO-d_6; 270MHz) δ (ppm): 7.93(1H, d, J = 16.3Hz), 7.57(1H, d, J = 8.9Hz), 6.88(1H, d, J = 8.9Hz), 6.82(1H, d, J = 16.3Hz), 3.98(2H, t, J = 7.1Hz), 3.86(2H, t, J = 7.3Hz), 3.81(3H, s), 2.32(3H, s), 2.09(3H, s), 1.80-1.55(4H, m), 0.95-0.80(6H, m)

Reference Example 11

(E)-8-(4-Methoxy-2,3-dimethylstyryl)-7-methyl-1,3-dipropylxanthine (Compound 14)

Substantially the same procedure as in Reference Example 1 was repeated using 4.00 g (5.10 mmol) of Compound 13 obtained in Reference Example 10 in place of Compound B to give 1.73 g (yield 83%) of Compound 14 as yellow needles.
Melting Point: 171.0-173.5 °C

Elemental Analysis: $C_{23}H_{30}N_4O_3$			
Calcd. (%):	C, 67.29;	H, 7.36;	N, 13.64
Found (%):	C, 66.87;	H, 7.67;	N, 13.51

IR (KBr) ν_{max} (cm^{-1}): 1697, 1659, 1593, 1493

NMR ($CDCl_3$; 270MHz) δ (ppm): 8.07(1H, d, J=15.3Hz), 7.46(1H, d, J=8.4Hz), 6.77(1H, d, J=8.4Hz), 6.67(1H, d, J=15.3Hz), 4.12(2H, t, J=7.3Hz), 4.03(3H, s), 3.98(2H, t, J=7.3Hz), 3.86(3H, s), 2.39(3H, s), 2.26(3H, s), 1.85-1.50(4H, m), 1.05-0.90(6H, m)

Reference Example 12

(E)-8-(2,4-Dimethoxy-3-methylstyryl)-1,3-dipropylxanthine (Compound 15)

Substantially the same procedure as in Reference Example 1 was repeated using 1.25 g (5.52 mmol) of 5,6-diamino-1,3-dipropyluracil and 1.35 g (6.08 mmol) of 2,4-dimethoxy-3-methylcinnamic acid. Then, the resultant crude crystals were recrystallized from dioxane/water to give 1.14 g (yield 50%) of Compound 15 as white needles.

Melting Point: 255.2-256.0 • C

Elemental Analysis: $C_{22}H_{28}N_4O_4$			
Calcd. (%):	C, 64.06;	H, 6.84;	N, 13.58
Found (%):	C, 63.77;	H, 7.01;	N, 13.42

IR (KBr) ν_{max} (cm^{-1}): 1694, 1650, 1594, 1495

NMR (DMSO-d_6; 270MHz) δ (ppm): 13.54(1H, brs), 7.76 (1H, d, J=16.5Hz), 7.59(1H, d, J=8.9Hz), 6.99(1H, d, J=16.5Hz), 6.84(1H, d, J=8.9Hz), 3.99(2H, t, J=7.4Hz), 3.85(2H, t, J=7.3Hz), 3.83(3H, s), 3.70 (3H, s), 2.09-(3H, s), 1.80-1.55(4H, m), 0.95-0.80(6H, m)

Reference Example 13

(E)-8-(2,4-Dimethoxy-3-methylstyryl)-7-methyl-1,3-dipropylxanthine (Compound 16)

Substantially the same procedure as in Reference Example 1 was repeated using 1.10 g (2.67 mmol) of Compound 15 obtained in Reference Example 12 in place of Compound B. Then, the resultant crude crystals were recrystallized from ethanol/2-propanol to give 620 mg (yield 55%) of Compound 16 as pale yellow grains.

Melting Point: 191.4-191.8 • C

Elemental Analysis: $C_{23}H_{30}N_4O_4$			
Calcd. (%):	C, 64.76;	H, 7.08;	N, 13.13
Found (%):	C, 64.84;	H, 7.30;	N, 12.89

IR (KBr) ν_{max} (cm^{-1}): 1695, 1654, 1274, 1107

NMR ($CDCl_3$; 270MHz) δ (ppm): 7.91(1H, d, J=15.8Hz), 7.42(1H, d, J=8.6Hz), 6.98(1H, d, J=15.8Hz), 6.69 (1H, d, J=8.6Hz), 4.11(2H, t, J=7.4Hz), 4.03(3H, s), 4.03-3.95(2H, m), 3.87(3H, s), 3.77(3H, s), 2.19(3H, s), 1.85-1.55-(4H, m), 1.03-0.94(6H, m)

Reference Example 14

(E)-8-[2-(1,4-Benzodioxan-6-yl)vinyl]-1,3-dipropylxanthine (Compound 17)

Substantially the same procedure as in Reference Example 1 was repeated using 1.35 g (5.96 mmol) of 5,6-diamino-1,3-dipropyluracil and 1.35 g (6.55 mmol) of 3-(1,4-benzodioxan-6-yl)acrylic acid. Then, the resultant crude crystals were recrystallized from ethanol/water to give 1.54 g (yield 65%) of Compound 17 as white needles.

Melting Point: >275 °C

Elemental Analysis: $C_{21}H_{24}N_4O_4$			
Calcd. (%):	C, 63.62;	H, 6.10;	N, 14.13
Found (%):	C, 63.57;	H, 6.24;	N, 14.36

IR (KBr) ν_{max} (cm^{-1}): 1693, 1636, 1582, 1511

NMR (DMSO-d_6; 270MHz) δ (ppm): 12.52(1H, brs), 7.63 (1H, d, J = 16.2Hz), 7.10-7.06(2H, m), 6.95-6.86(2H, m), 4.29(4H, s), 4.15-4.10(4H, m), 1.90-1.65(4H, m), 1.05-0.95(6H, m)

Reference Example 15

(E)-8-[2-(1,4-Benzodioxan-6-yl)vinyl]-7-methyl-1,3-dipropylxanthine (Compound 18)

Substantially the same procedure as in Reference Example 1 was repeated using 1.0 g (2.52 mmol) of Compound 17 obtained in Reference Example 14 in place of Compound B. Then, the resultant crude crystals were recrystallized from ethanol to give 840 mg (yield 81%) of Compound 18 as pale yellow needles.

Melting Point: 181.9-182.3 °C

Elemental Analysis: $C_{22}H_{26}N_4O_4$			
Calcd. (%):	C, 64.37;	H, 6.38;	N, 13.64
Found (%):	C, 64.56;	H, 6.63;	N, 13.92

IR (KBr) ν_{max} (cm^{-1}): 1693, 1651, 1510, 1288

NMR ($CDCl_3$; 270MHz) δ (ppm): 7.67(1H, d, J = 15.5Hz), 7.10(2H, m), 6.88(1H, d, J = 8.3Hz), 6.74(1H, d, J = 15.5Hz), 4.30(4H, m), 4.13-3.95(4H, m), 4.03(3H, s), 1.88-1.65(4H, m), 1.03-0.94(6H, m)

Reference Example 16

(E)-8-(3,4-Methylenedioxystyryl)-1,3-dipropylxanthine (Compound 19)

Substantially the same procedure as in Reference Example 1 was repeated using 4.25 g (18.8 mmol) of 5,6-diamino-1,3-dipropyluracil and 4.33 g (22.6 mmol) of 3,4-methylenedioxycinnamic acid. Then, the resultant crude crystals were recrystallized from dioxane to give 4.92 g (yield 69%) of Compound 19 as a pale yellow powder.

Melting Point: >270 °C

Elemental Analysis: $C_{20}H_{22}N_4O_4 \cdot 0.75H_2O$			
Calcd. (%):	C, 60.50;	H, 5.72;	N, 14.43
Found (%):	C, 60.67;	H, 5.98;	N, 14.15

IR (KBr) ν_{max} (cm^{-1}): 1688, 1648, 1499

NMR (DMSO-d_6; 270MHz) δ (ppm): 13.49(1H, brs), 7.56 (1H, d, J=16.3Hz), 7.30(1H, s), 7.07(1H, d, J=8.4Hz), 6.97-6.89(2H, m), 6.07(2H, s), 3.98 (2H, t, J=7.2Hz), 3.85(2H, t, J=7.3Hz), 1.75-1.35(4H, m), 0.95-0.80(6H, m)

Reference Example 17

(E)-7-Methyl-8-(3,4-methylenedioxystyryl)-1,3-dipropylxanthine (Compound 20)

Substantially the same procedure as in Reference Example 1 was repeated using 3.0 g (7.85 mmol) of Compound 19 obtained in Reference Example 16 in place of Compound B. Then, the resultant crude crystals were recrystallized from toluene/cyclohexane to give 2.33 g (yield 75%) of Compound 20 as a pale green powder.

Melting Point: 151.7-155.4 °C

Elemental Analysis: $C_{21}H_{24}N_4O_4 \cdot 0.25H_2O$			
Calcd. (%):	C, 62.91;	H, 6.16;	N, 13.97
Found (%):	C, 62.88;	H, 6.25;	N, 13.72

IR (KBr) ν_{max} (cm^{-1}): 1689, 1650, 1498, 1443

NMR ($CDCl_3$; 270MHz) δ (ppm): 7.70(1H, d, J=15.6Hz), 7.10-6.95(2H, m), 6.84(1H, d, J=7.9Hz), 6.72(1H, d, J=15.6Hz), 6.02(2H, s), 4.10(2H, t, J=7.3Hz), 4.04(3H, s), 3.97(2H, t, J=7.3Hz), 1.90-1.65(4H, m), 1.05-0.90(6H, m)

Reference Example 18

(E)-1,3-Dipropyl-8-(2,3,4-trimethoxystyryl)xanthine (Compound 21)

Substantially the same procedure as in Reference Example 1 was repeated using 2.00 g (8.85 mmol) of 5,6-diamino-1,3-dipropyluracil and 2.32 g (9.73 mmol) of 2,3,4-trimethoxycinnamic acid. Then, the resultant crude crystals were recrystallized from 2-propanol/water to give 1.84 g (yield 49%) of Compound 21 as pale yellow needles.

Melting Point: 246.5-246.8 °C

Elemental Analysis: $C_{22}H_{28}N_4O_5$			
Calcd. (%):	C, 61.66;	H, 6.58;	N, 13.07
Found (%):	C, 61.50;	H, 6.89;	N, 13.06

IR (KBr) ν_{max} (cm^{-1}): 1703, 1651, 1504

NMR ($CDCl_3$; 270MHz) δ (ppm): 12.72(1H, brs), 7.92 (1H, d, J=16.5Hz), 7.31(1H, d, J=8.7Hz), 7.09-(1H, d, J=16.5Hz), 6.71(1H, d, J=8.7Hz), 4.25-4.10(4H, m), 3.95(3H, s), 3.91(3H, s), 3.90(3H, s), 2.00-1.65(4H, m), 1.10-0.85(6H, m)

Reference Example 19

(E)-7-Methyl-1,3-dipropyl-8-(2,3,4-trimethoxystyryl)xanthine (Compound 22)

Substantially the same procedure as in Reference Example 1 was repeated using 2.50 g (5.84 mmol) of Compound 21 obtained in Reference Example 18 in place of Compound B. Then, the resultant crude crystals were recrystallized from ethanol to give 1.70 g (yield 66%) of Compound 22 as yellow needles.

Melting Point: 153.5-153.8 • C

Elemental Analysis: $C_{23}H_{30}N_4O_5$			
Calcd. (%):	C, 62.42;	H, 6.83;	N, 12.66
Found (%):	C, 62.77;	H, 7.25;	N, 12.65

IR (KBr) ν_{max} (cm^{-1}): 1699, 1657, 1590, 1497, 1439

NMR ($CDCl_3$; 270MHz) δ (ppm): 7.88(1H, d, J=15.8Hz), 7.28(1H, d, J=8.9Hz), 7.02(1H, d, J=15.8Hz), 6.71 (1H, d, J=8.9Hz), 4.25-3.95(4H, m), 4.03(3H, s), 3.97(3H, s), 3.91(3H, s), 3.90(3H, s), 2.00-1.65 (4H, m), 1.10-0.85(6H, m)

Reference Example 20

(E)-1,3-Dipropyl-8-(2,4,5-trimethoxystyryl)xanthine (Compound 23)

Substantially the same procedure as in Reference Example 1 was repeated using 2.00 g (8.85 mmol) of 5,6-diamino-1,3-dipropyluracil and 2.32 g (9.73 mmol) of 2,4,5-trimethoxycinnamic acid. Then, the resultant crude crystals were recrystallized from 2-propanol/water to give 870 mg (yield 23%) of Compound 23 as a pale yellow powder.

Melting Point: 254.5-255.7 • C

Elemental Analysis: $C_{22}H_{28}N_4O_5$			
Calcd. (%):	C, 61.66;	H, 6.58;	N, 13.07
Found (%):	C, 61.94;	H, 6.97;	N, 13.06

IR (KBr) ν_{max} (cm^{-1}): 1693, 1650, 1517

NMR ($CDCl_3$; 270MHz) δ (ppm): 12.53(1H, brs), 7.97 (1H, d, J=16.5Hz), 7.10(1H, s), 6.99(1H, d, J=16.5Hz), 6.54(1H, s), 4.25-4.10(4H, m), 3.95(3H, s), 3.90(6H, s), 1.90-1.65(4H, m), 1.01(3H, t, J=7.6Hz), 0.86(3H, t, J=7.6Hz)

Reference Example 21

(E)-7-Methyl-1,3-dipropyl-8-(2,4,5-trimethoxystyryl)xanthine (Compound 24)

Substantially the same procedure as in Reference Example 1 was repeated using 0.5 g (1.17 mmol) of Compound 23 obtained in Reference Example 20 in place of Compound B. Then, the resultant crude crystals were recrystallized from toluene/hexane to give 200 mg (yield 39%) of Compound 24 as a pale yellow powder.

Melting Point: 195.5-196.2 • C

Elemental Analysis: $C_{23}H_{30}N_4O_5$			
Calcd. (%):	C, 62.42;	H, 6.83;	N, 12.66
Found (%):	C, 62.14;	H, 7.12;	N, 12.56

IR (KBr) ν_{max} (cm^{-1}): 1688, 1653, 1515, 1439, 1214

NMR ($CDCl_3$; 270MHz) δ (ppm): 7.93(1H, d, J=15.8Hz), 7.05(1H, s), 6.94(1H, d, J=15.8Hz), 6.54(1H, s), 4.15-3.90(4H, m), 4.04(3H, s), 3.95(3H, s), 3.93 (3H, s), 3.91(3H, s), 1.90-1.65(4H, m), 1.03-0.94 (6H, m)

Reference Example 22

(E)-8-(2,4-Dimethoxystyryl)-1,3-dipropylxanthine (Compound 25)

Substantially the same procedure as in Reference Example 1 was repeated using 3.0 g (13.3 mmol) of 5,6-diamino-1,3-dipropyluracil and 3.04 g (14.60 mmol) of 2,4-dimethoxycinnamic acid. Then, the resultant crude crystals were recrystallized from dioxane/water to give 1.26 g (yield 24%) of Compound 25 as white crystals.

Melting Point: 273.1-273.7 • C

Elemental Analysis: $C_{21}H_{26}N_4O_4$			
Calcd. (%):	C, 63.30;	H, 6.57;	N, 14.06
Found (%):	C, 62.94;	H, 6.78;	N, 14.03

IR (KBr) ν_{max} (cm^{-1}): 1693, 1645, 1506

NMR (DMSO-d_6; 270MHz) δ (ppm): 13.39(1H, brs), 7.78 (1H, d, J = 16.5Hz), 7.54(1H, d, J = 8.2Hz), 6.95(1H, d, J = 16.5Hz), 6.63(1H, d, J = 2.3Hz), 6.00(1H, dd, J = 8.2, 2.3Hz), 4.01-3.85(4H, m), 3.89(3H, s), 3.82 (3H, s), 1.79-1.50(4H, m), 0.93-0.87(6H, m)

Reference Example 23

(E)-8-(2,4-Dimethoxystyryl)-7-methyl-1,3-dipropylxanthine (Compound 26)

Substantially the same procedure as in Reference Example 1 was repeated using 600 mg (1.51 mmol) of Compound 25 obtained in Reference Example 22 in place of Compound B. Then, the resultant crude crystals were recrystallized from hexane/ethyl acetate to give 556 mg (yield 90%) of Compound 26 as brown needles.

Melting Point: 167.6-167.9 • C

Elemental Analysis: $C_{22}H_{28}N_4O_4$			
Calcd. (%):	C, 64.06;	H, 6.84;	N, 13.58
Found (%):	C, 63.98;	H, 6.94;	N, 13.61

IR (KBr) ν_{max} (cm^{-1}): 1691, 1653, 1603, 1437

NMR ($CDCl_3$; 270MHz) δ (ppm): 7.92(1H, d, J = 15.8Hz), 7.48(1H, d, J = 8.6Hz), 6.98(1H, d, J = 15.8Hz), 6.54 (1H, dd, J = 8.6, 2.3Hz), 6.50(1H, d, J = 2.3Hz), 4.14-3.95(4H, m), 4.02(3H, s), 3.93(3H, s), 3.86 (3H, s), 1.91-1.65(4H, m), 1.03-0.94(6H, m)

Reference Example 24

(E)-8-(4-Benzyloxy-3,5-dimethoxystyryl)-1,3-dipropylxanthine (Compound 27)

A mixture of 5.0 g (22.3 mmol) of 4-hydroxy-3,5-dimethoxycinnamic acid, 8.0 ml (66.9 mmol) of benzyl bromide, and potassium carbonate was stirred in 50 ml of dimethylformamide at 70 • C for 2 hours. Insoluble matters were filtered off and the filtrate was poured into 500 ml of water. The mixture was extracted three times with 100 ml of chloroform. The extract was washed twice with water and twice with a saturated aqueous solution of sodium chloride, and dried over anhydrous sodium sulfate, followed by evaporation under reduced pressure. To the residue were added 50 ml of an aqueous 2N sodium hydroxide solution and 50 ml of ethanol, followed by heating under reflux for 15 minutes. After cooling, the solution was adjusted to pH 3 with a concentrated hydrochloric acid solution and extracted three times with 50 ml of chloroform. The extract was washed with a saturated aqueous solution of sodium chloride, and dried over anhydrous sodium sulfate, followed by evaporation under reduced pressure. The residue was recrystallized from hexane to give 5.4 g (yield 77%) of (E)-4-benzyloxy-3,5-dimethoxycinnamic acid (Compound H) as

pale yellow needles.
Melting Point: 101.8-102.3 °C

Elemental Analysis: $C_{18}H_{18}O_5$		
Calcd. (%):	C, 68.77;	H, 5.77
Found (%):	C, 68.95;	H, 5.79

IR (KBr) ν_{max} (cm^{-1}): 2900(br), 1683, 1630, 1579, 1502, 1281, 1129
NMR ($CDCl_3$; 90MHz) δ (ppm): 7.80(1H, d, J=16Hz), 7.55-7.20(5H, m), 6.80(2H, s), 6.30(1H, d, J=16Hz), 5.08(2H, s)

Substantially the same procedure as in Reference Example 1 was repeated using 3.30 g (14.5 mmol) of 5,6-diamino-1,3-dipropyluracil and 5.0 g (15.9 mmol) of Compound H. Then, the resultant crude crystals were recrystallized from ethanol/2-propanol to give 5.44 g (yield 74%) of Compound 27 as a white powder.
Melting Point: 221.1-221.4 °C

Elemental Analysis: $C_{28}H_{32}N_4O_5$			
Calcd. (%):	C, 66.65;	H, 6.39;	N, 11.10
Found (%):	C, 66.65;	H, 6.51;	N, 11.01

IR (KBr) ν_{max} (cm^{-1}): 1704, 1637, 1582, 1505
NMR ($CDCl_3$; 90MHz) δ (ppm): 7.69(1H, d, J=16Hz), 7.55-7.20(5H, m), 6.96(1H, d, J=16Hz), 6.80-(2H, s), 5.08(2H, s), 4.25-3.95(4H, m), 3.88(6H, s), 2.10-1.65(4H, m), 1.20-0.80(6H, m)

Reference Example 25

(E)-8-(4-Benzyloxy-3,5-dimethoxystyryl)-7-methyl-1,3-dipropylxanthine (Compound 28)

Substantially the same procedure as in Reference Example 1 was repeated using 8.20 g (14.5 mmol) of Compound 27 obtained in Reference Example 24 in place of Compound B. Then, the resultant crude crystals were recrystallized from 2-propanol/water to give 4.78 g (yield 64%) of Compound 28 as a white powder.
Melting Point: 164.7-165.1 °C

Elemental Analysis: $C_{29}H_{34}N_4O_5$			
Calcd. (%):	C, 67.16;	H, 6.60;	N, 10.80
Found (%):	C, 67.01;	H, 6.61;	N, 10.70

IR (KBr) ν_{max} (cm^{-1}): 1695, 1659, 1580, 1542, 1505, 1455, 1335
NMR ($CDCl_3$; 90MHz) δ (ppm): 7.70(1H, d, J=16Hz), 7.55-7.20(5H, m), 6.78(2H, s), 6.72(1H, d, J=16Hz), 5.07(2H, s), 4.25-3.95(4H, m), 4.07(3H, s), 3.89(6H, s), 2.10-1.65(4H, m), 1.20-0.85(6H, m)

Reference Example 26

(E)-8-(2,3-Dimethoxystyryl)-1,3-dipropylxanthine (Compound 29)

Substantially the same procedure as in Reference Example 1 was repeated using 2.0 g (8.85 mmol) of 5,6-diamino-1,3-dipropyluracil and 2.2 g (10.6 mmol) of 2,3-dimethoxycinnamic acid. Then, the resultant crude crystals were recrystallized from chloroform/cyclohexane to give 1.26 g (yield 36%) of Compound 29 as yellow crystals.
Melting Point: 236.0-236.5 °C

Elemental Analysis: $C_{21}H_{26}N_4O_4$			
Calcd. (%):	C, 63.30;	H, 6.57;	N, 14.06
Found (%):	C, 62.99;	H, 6.71;	N, 13.83

IR (KBr) ν_{max} (cm^{-1}): 1701, 1652, 1271

NMR (DMSO-d_6; 270MHz) δ (ppm): 13.63 (1H, brs), 7.84 (1H, d, J=16.8Hz), 7.28(1H, d, J=6.8Hz), 7.14-7.05 (3H, m), 4.00(2H, t, J=7.3Hz), 3.88-3.78(2H, m), 3.83-(3H, s), 3.79(3H, s), 1.80-1.50(4H, m), 0.93-0.85(6H, m)

Reference Example 27

(E)-8-(2,3-Dimethoxystyryl)-7-methyl-1,3-dipropylxanthine (Compound 30)

Substantially the same procedure as in Reference Example 1 was repeated using 1.5 g (3.77 mmol) of Compound 29 obtained in Reference Example 26 in place of Compound B. Then, the resultant crude crystals were recrystallized from toluene/cyclohexane to give 1.22 g (yield 79%) of Compound 30 as pale brown needles.

Melting Point: 163.5-163.7 °C

Elemental Analysis: $C_{22}H_{28}N_4O_4$			
Calcd. (%):	C, 64.06;	H, 6.84;	N, 13.58
Found (%):	C, 64.03;	H, 7.12;	N, 13.42

IR (KBr) ν_{max} (cm^{-1}): 1695, 1657, 1272

NMR (DMSO-d_6; 270MHz) δ (ppm): 7.88(1H, d, J=15.8Hz), 7.50(1H, dd, J=1.7, 7.6Hz), 7.32(1H, d, J=15.8Hz), 7.17-7.06(2H, m), 4.02(3H, s), 4.02-3.98(2H, m), 3.86-3.81(2H, m), 3.84(3H, s), 3.79(3H, s), 1.80-1.65(2H, m), 1.65-1.50-(2H, m), 0.93-0.84(6H, m)

Reference Example 28

(E)-8-(3,4-Dimethylstyryl)-1,3-dipropylxanthine (Compound 31)

Substantially the same procedure as in Reference Example 1 was repeated using 5.90 g (26.0 mmol) of 5,6-diamino-1,3-dipropyluracil and 5.5 g (31.3 mmol) of 3,4-dimethylcinnamic acid. Then, the resultant crude crystals were recrystallized from dioxane/water to give 7.70 g (yield 81%) of Compound 31 as a white powder.

Melting Point: 252.7-254.0 °C

Elemental Analysis: $C_{21}H_{26}N_4O_2$			
Calcd. (%):	C, 68.83;	H, 7.15;	N, 15.29
Found (%):	C, 68.43;	H, 7.22;	N, 15.22

IR (KBr) ν_{max} (cm^{-1}): 1700, 1648, 1490

NMR (DMSO-d_6; 270MHz) δ (ppm): 7.40(1H, d, J=16.2Hz), 7.37(1H, s), 7.29(1H, d, J=7.2Hz), 7.14-(1H, d, J=7.2Hz), 6.95(1H, d, J=16.2Hz), 3.95(2H, t, J=7.2Hz), 3.83(2H, t, J=7.4Hz), 2.25(3H, s), 2.23 (3H, s), 1.80-1.55(4H, m), 1.00-0.90(6H, m)

Reference Example 29

(E)-8-(3,4-Dimethylstyryl)-7-methyl-1,3-dipropylxanthine (Compound 32)

Substantially the same procedure as in Reference Example 1 was repeated using 6.50 g (17.8 mmol) of Compound 31 obtained in Reference Example 28 in place of Compound B. Then, the resultant crude crystals were recrystallized from ethanol/water to give 5.62 g (yield 83%) of Compound 32 as white needles.

Melting Point: 169.3-170.3 °C

Elemental Analysis: $C_{22}H_{28}N_4O_2$			
Calcd. (%):	C, 69.45;	H, 7.42;	N, 14.72
Found (%):	C, 69.33;	H, 7.42;	N, 14.86

IR (KBr) ν_{max} (cm^{-1}): 1693, 1656

NMR (DMSO-d_6; 270MHz) δ (ppm): 7.59(1H, d, J=15.8Hz), 7.58(1H, s), 7.49(1H, d, J=7.6Hz), 7.26-(1H, d, J=15.8Hz), 7.19(1H, d, J=7.6Hz), 4.02(3H, s), 4.05-3.90-(2H, m), 3.84(2H, t, J=7.4Hz), 2.27(3H, s), 2.25(3H, s), 1.85-1.50-(4H, m), 1.00-0.85(6H, m)

Reference Example 30

(E)-8-(3,5-Dimethoxystyryl)-1,3-dipropylxanthine (Compound 33)

Substantially the same procedure as in Reference Example 1 was repeated using 3.95 g (17.5 mmol) of 5,6-diamino-1,3-dipropyluracil and 4.0 g (19.2 mmol) of 3,5-dimethoxycinnamic acid. Then, the resultant crude crystals were recrystallized from dimethylformamide/water to give 3.78 g (yield 54%) of Compound 33 as a white powder.

Melting Point: 248.7-250.3 °C

Elemental Analysis: $C_{21}H_{26}N_4O_4$			
Calcd. (%):	C, 63.30;	H, 6.58;	N, 14.06
Found (%):	C, 63.02;	H, 6.71;	N, 14.06

IR (KBr) ν_{max} (cm^{-1}): 1687, 1631, 1588, 1494

NMR (DMSO-d_6; 270MHz) δ (ppm): 7.56(1H, d, J=16.6Hz), 7.08(1H, d, J=16.6Hz), 6.78(2H, d, J=2.0Hz), 6.50 (1H, t, J=2.0Hz), 3.98(2H, t, J=7.3Hz), 3.85(2H, t, J=7.3Hz), 3.79(6H, s), 1.80-1.50(4H, m), 0.92-0.84(6H, m)

Reference Example 31

(E)-8-(3,5-Dimethoxystyryl)-7-methyl-1,3-dipropylxanthine (Compound 34)

Substantially the same procedure as in Reference Example 1 was repeated using 3.23 g (8.27 mmol) of Compound 33 obtained in Reference Example 30 in place of Compound B. Then, the resultant crude crystals were recrystallized from acetonitrile to give 2.96 g (yield 87%) of Compound 34 as white needles.

Melting Point: 178.0-178.2 °C

Elemental Analysis: $C_{22}H_{28}N_4O_4$			
Calcd. (%):	C, 64.06;	H, 6.84;	N, 13.58
Found (%):	C, 63.87;	H, 7.11;	N, 13.66

IR (KBr) ν_{max} (cm^{-1}): 1692, 1657, 1592

NMR (DMSO-d_6; 270MHz) δ (ppm): 7.59(1H, d, J=15.9Hz), 7.35(1H, d, J=15.9Hz), 6.98(2H, d, J=2.9Hz), 6.51 (1H, t, J=2.9Hz), 4.04(3H, s), 4.10-3.95(2H, m), 3.90-3.75(2H, m), 3.80(6H, s), 1.80-1.50(4H, m), 1.00-0.80(6H, m)

Reference Example 32

(E)-8-(3-Nitrostyryl)-1,3-dipropylxanthine (Compound 35)

Substantially the same procedure as in Reference Example 1 was repeated using 4.0 g (17.7 mmol) of 5,6-diamino-1,3-dipropyluracil and 3.8 g (19.5 mmol) of 3-nitrocinnamic acid. Then, the resultant crude crystals were recrystallized from toluene to give 3.86 g (yield 57%) of Compound 35 as pale yellow needles.

Melting Point: 256.5-256.8 • C

Elemental Analysis: $C_{19}H_{21}N_5O_4 \cdot 0.25C_6H_5CH_3$			
Calcd. (%):	C, 61.32;	H, 5.70;	N, 17.23
Found (%):	C, 61.64;	H, 5.94;	N, 17.29

IR (KBr) ν_{max} (cm^{-1}): 1701, 1649, 1529, 1355

NMR (DMSO-d_6; 270MHz) δ (ppm): 8.42(1H, s), 8.19(1H, d, J=8.0Hz), 8.12(1H, d, J=7.6Hz), 7.80-7.65(2H, m), 7.25(1H, d, J=16.5Hz), 4.00(2H, t, J=7.2Hz), 3.86-(2H, t, J=7.3Hz), 1.80-1.55(4H, m), 1.00-0.80(6H, m)

Reference Example 33

(E)-7-Methyl-8-(3-nitrostyryl)-1,3-dipropylxanthine (Compound 36)

Substantially the same procedure as in Reference Example 1 was repeated using 3.20 g (8.36 mmol) of Compound 35 obtained in Reference Example 32 in place of Compound B. Then, the resultant crude crystals were recrystallized from toluene/cyclohexane to give 2.41 g (yield 73%) of Compound 36 as yellow needles.

Melting Point: 218.2-218.4 • C

Elemental Analysis: $C_{20}H_{23}N_5O_4$			
Calcd. (%):	C, 60.44;	H, 5.83;	N, 17.62
Found (%):	C, 59.94;	H, 5.97;	N, 17.43

IR (KBr) ν_{max} (cm^{-1}): 1699, 1662, 1521

NMR (DMSO-d_6; 270MHz) δ (ppm): 8.70(1H, m), 8.24(1H, d, J=7.9Hz), 8.19(1H, dd, J=1.6, 7.6Hz), 7.78(1H, d, J=15.9Hz), 7.71(1H, t, J=7.9Hz), 7.61(1H, d, J=15.9Hz), 4.08(3H, s), 4.01(2H, t, J=7.3Hz), 3.85 (2H, t, J=7.3Hz), 1.85-1.55(4H, m), 0.91(3H, t, J=7.5Hz), 0.87(3H, t, J=7.4Hz)

Reference Example 34

(E)-8-(3-Fluorostyryl)-1,3-dipropylxanthine (Compound 37)

Substantially the same procedure as in Reference Example 1 was repeated using 3.95 g (17.5 mmol) of 5,6-diamino-1,3-dipropyluracil and 3.19 g (19.2 mmol) of 3-fluorocinnamic acid. Then, the resultant crude crystals were recrystallized from dimethylformamide/water to give 4.67 g (yield 75%) of Compound 37 as a pale yellow powder.

Melting Point: 265.0-265.9 °C

Elemental Analysis: $C_{19}H_{21}N_4O_2F$			
Calcd. (%):	C, 64.03;	H, 5.94;	N, 15.72
Found (%):	C, 64.02;	H, 5.96;	N, 15.46

IR (KBr) ν_{max} (cm^{-1}): 1701, 1646

NMR (DMSO-d_6; 270MHz) δ (ppm): 7.63(1H, d, J=16.3Hz), 7.53-7.41(3H, m), 7.23-7.15(1H, m), 7.12-(1H, d, J=16.3Hz), 3.99(2H, t, J=7.0Hz), 3.86(2H, t, J=7.3Hz), 1.80-1.50(4H, m), 0.93-0.85(6H, m)

Reference Example 35

(E)-8-(3-Fluorostyryl)-7-methyl-1,3-dipropylxanthine (Compound 38)

Substantially the same procedure as in Reference Example 1 was repeated using 2.92 g (8.19 mmol) of Compound 37 obtained in Reference Example 34 in place of Compound B. Then, the resultant crude crystals were recrystallized from toluene/cyclohexane to give 2.67 g (yield 88%) of Compound 38 as pale yellow needles.

Melting Point: 161.9-162.0 °C

Elemental Analysis: $C_{20}H_{23}N_4O_2F$			
Calcd. (%):	C, 64.85;	H, 6.26;	N, 15.12
Found (%):	C, 64.61;	H, 6.40;	N, 14.86

IR (KBr) ν_{max} (cm^{-1}): 1693, 1656, 1544

NMR (DMSO-d_6; 270MHz) δ (ppm): 7.80-7.60(3H, m), 7.50-7.38(2H, m), 7.19(1H, dt, J=2.3, 8.3Hz), 4.04(3H, s), 4.00(2H, t, J=7.3Hz), 3.84(2H, t, J=7.5Hz), 1.80-1.55(4H, m), 1.00-0.80(6H, m)

Reference Example 36

(E)-8-(3-Chlorostyryl)-1,3-dipropylxanthine (Compound 39)

Substantially the same procedure as in Reference Example 1 was repeated using 3.95 g (17.5 mmol) of 5,6-diamino-1,3-dipropyluracil and 3.51 g (19.2 mmol) of 3-chlorocinnamic acid. Then, the resultant crude crystals were recrystallized from dimethylformamide/water to give 4.44 g (yield 67%) of Compound 39 as pale yellow crystals.

Melting Point: 258.9-259.4 °C

Elemental Analysis: $C_{19}H_{21}N_4O_2Cl$			
Calcd. (%):	C, 61.21;	H, 5.68;	N, 15.03
Found (%):	C, 61.52;	H, 5.73;	N, 14.79

IR (KBr) ν_{max} (cm^{-1}): 1700, 1644, 1588, 1494
NMR (DMSO-d_6; 270MHz) δ (ppm): 13.7(1H, brs), 7.71-7.52(3H, m), 7.48-7.39(2H, m), 7.12(1H, d, J=16.3Hz), 3.99(2H, t, J=7.0Hz), 3.86(2H, t, J=7.0Hz), 1.80-1.50(4H, m), 0.93-0.84(6H, m)

Reference Example 37

(E)-8-(3-Chlorostyryl)-7-methyl-1,3-dipropylxanthine (Compound 40)

Substantially the same procedure as in Reference Example 1 was repeated using 2.85 g (7.66 mmol) of Compound 39 obtained in Reference Example 36 in place of Compound B. Then, the resultant crude crystals were recrystallised from ethanol to give 2.69 g (yield 91%) of Compound 40 as white needles.
Melting Point: 167.7-167.9 • C

Elemental Analysis: $C_{20}H_{23}N_4O_2Cl$			
Calcd. (%):	C, 62.09;	H, 5.99;	N, 14.48
Found (%):	C, 62.00;	H, 6.08;	N, 14.27

IR (KBr) ν_{max} (cm^{-1}): 1691, 1657, 1543
NMR (DMSO-d_6; 270MHz) δ (ppm): 7.99(1H, s), 7.72 (1H, d, J=6.6Hz), 7.63(1H, d, J=15.8Hz), 7.50-7.30(3H, m), 4.05(3H, s), 4.00(2H, t, J=7.5Hz), 3.84(2H, t, J=7.4Hz), 1.80-1.55(4H, m), 1.00-0.80(6H, m)

Reference Example 38

(E)-8-(2-Chlorostyryl)-1,3-dipropylxanthine (Compound 41)

Substantially the same procedure as in Reference Example 1 was repeated using 3.00 g (13.3 mmol) of 5,6-diamino-1,3-dipropyluracil and 2.67 g (14.6 mmol) of 2-chlorocinnamic acid. Then, the resultant crude crystals were recrystallized from toluene to give 3.72 g (yield 82%) of Compound 41 as white needles.
Melting Point: 269.4-269.9 • C

Elemental Analysis: $C_{19}H_{21}N_4O_2Cl$			
Calcd. (%):	C, 61.21;	H, 5.68;	N, 15.03
Found (%):	C, 60.94;	H, 5.69;	N, 14.68

IR (KBr) ν_{max} (cm^{-1}): 1695, 1645, 1493
NMR (DMSO-d_6; 270MHz) δ (ppm): 8.00-7.80(2H, m), 7.55-7.50(1H, m), 7.45-7.37(2H, m), 7.12(1H, d, J=16.5Hz), 3.99(2H, t, J=7.3Hz), 3.86(2H, t, J=7.4Hz), 1.80-1.55(4H, m), 1.00-0.80(6H, m)

Reference Example 39

(E)-8-(2-Chlorostyryl)-7-methyl-1,3-dipropylxanthine (Compound 42)

Substantially the same procedure as in Reference Example 1 was repeated using 2.37 g (6.37 mmol) of Compound 41 obtained in Reference Example 38 in place of Compound B. Then, the resultant crude crystals were recrystallized from ethanol/water to give 1.88 g (yield 77%) of Compound 42 as yellow needles.
Melting Point: 159.0-159.9 • C

Elemental Analysis: $C_{20}H_{23}N_4O_2Cl$			
Calcd. (%):	C, 62.09;	H, 5.99;	N, 14.48
Found (%):	C, 61.75;	H, 6.14;	N, 14.45

IR (KBr) ν_{max} (cm^{-1}): 1696, 1650, 1544

NMR (DMSO-d_6; 270MHz) δ (ppm): 8.10(1H, dd, J=2.3, 7.3Hz), 7.97(1H, d, J=15.5Hz), 7.55-7.50(1H, m), 7.46-7.35(3H, m), 4.05(3H, s), 4.00(2H, t, J=7.3Hz), 3.84(2H, t, J=7.3Hz), 1.80-1.55(4H, m), 1.00-0.80(6H, m)

Reference Example 40

(E)-8-(2-Fluorostyryl)-1,3-dipropylxanthine (Compound 43)

Substantially the same procedure as in Reference Example 1 was repeated using 3.00 g (13.3 mmol) of 5,6-diamino-1,3-dipropyluracil and 2.43 g (14.6 mmol) of 2-fluorocinnamic acid. Then, the resultant crude crystals were recrystallized from dioxane/water to give 3.23 g (yield 68%) of Compound 43 as white needles.

Melting Point: 258.8-259.2 °C

Elemental Analysis: $C_{19}H_{21}N_4O_2F$			
Calcd. (%):	C, 64.03;	H, 5.94;	N, 15.72
Found (%):	C, 64.01;	H, 6.11;	N, 15.52

IR (KBr) ν_{max} (cm^{-1}): 1702, 1648

NMR (DMSO-d_6; 270MHz) δ (ppm): 7.85-7.77(2H, m), 7.46-7.32(1H, m), 7.29-7.23(2H, m), 7.16(1H, d, J=16.5Hz), 3.99(2H, t, J=7.1Hz), 3.86(2H, t, J=7.3Hz), 1.80-1.55(4H, m), 1.00-0.80(6H, m)

Reference Example 41

(E)-8-(2-Fluorostyryl)-7-methyl-1,3-dipropylxanthine (Compound 44)

Substantially the same procedure as in Reference Example 1 was repeated using 3.50 g (9.83 mmol) of Compound 43 obtained in Reference Example 40 in place of Compound B. Then, the resultant crude crystals were recrystallized from ethanol/water to give 1.23 g (yield 34%) of Compound 44 as white needles.

Melting Point: 155.5-155.9 °C

Elemental Analysis: $C_{20}H_{23}N_4O_2F$			
Calcd. (%):	C, 64.85;	H, 6.26;	N, 15.12
Found (%):	C, 65.00;	H, 6.44;	N, 15.34

IR (KBr) ν_{max} (cm^{-1}): 1694, 1660

NMR (DMSO-d_6; 270MHz) δ (ppm): 8.02(1H, t, J=8.3Hz), 7.75(1H, d, J=15.5Hz), 7.47-7.40(2H, m), 7.40-7.25(2H, m), 4.03(3H, s), 4.00(2H, t, J=7.4Hz), 3.84(2H, t, J=7.4Hz), 1.80-1.55(4H, m), 1.00-0.80(6H, m)

Reference Example 42

(E)-8-(4-Methoxy-2,5-dimethylstyryl)-1,3-dipropylxanthine (Compound 45)

Substantially the same procedure as in Reference Example 1 was repeated using 2.5 g (11.1 mmol) of 5,6-diamino-1,3-dipropyluracil and 2.51 g (12.17 mmol) of 4-methoxy-2,5-dimethylcinnamic acid. Then, the resultant crude crystals were recrystallized from ethanol/water to give 1.98 g (yield 45%) of Compound 45

as white crystals.
Melting Point: 268.0-269.2 • C

Elemental Analysis: $C_{22}H_{28}N_4O_3$			
Calcd. (%):	C, 66.65;	H, 7.11;	N, 14.13
Found (%):	C, 66.82;	H, 7.34;	N, 14.14

IR (KBr) ν_{max} (cm^{-1}): 1694, 1644, 1506, 1261
NMR (DMSO-d_6; 270MHz) δ (ppm): 12.95(1H, brs), 7.95 (1H, d, J=15.8Hz), 7.42(1H, s), 6.89(1H, d, J=15.8Hz), 6.66(1H, s), 4.19-4.07(4H, m), 3.86(3H, s), 2.48(3H, s), 2.21(3H, s), 1.91-1.74(4H, m), 1.02(3H, t, J=6.9Hz), 0.93(3H, t, J=6.9Hz)

Reference Example 43

(E)-8-(4-Methoxy-2,5-dimethylstyryl)-7-methyl-1,3-dipropylxanthine (Compound 46)

Substantially the same procedure as in Reference Example 1 was repeated using 973 mg (2.45 mmol) of Compound 45 obtained in Reference Example 42 in place of Compound B. Then, the resultant crude crystals were recrystallized from 2-propanol/water to give 966 mg (yield 96%) of Compound 46 as pale yellow needles.
Melting Point: 245.3-246.3 • C

Elemental Analysis: $C_{23}H_{30}N_4O_3$			
Calcd. (%):	C, 67.30;	H, 7.36;	N, 13.65
Found (%):	C, 67.37;	H, 7.51;	N, 13.69

IR (KBr) ν_{max} (cm^{-1}): 1690, 1655, 1508, 1261
NMR (DMSO-d_6; 270MHz) δ (ppm): 7.96(1H, d, J=15.8Hz), 7.41(1H, s), 6.70(1H, d, J=15.8Hz), 6.66-(1H, s), 4.14-4.09(2H, m), 4.05(3H, s), 4.01-3.95(2H, m) 2.48(3H, s), 2.22(3H, s), 1.91-1.77(2H, m), 1.74-1.63(2H, m), 1.03-0.94(6H, m)

Reference Example 44

(Z)-8-(3,4-Dimethoxystyryl)-7-methyl-1,3-dipropylxanthine (Compound 47) (an about 6 : 4 mixture of Compound 47 and Compound 1)

Compound 1 (2.00 g, 4.85 mmol) obtained in Reference Example 1 was dissolved in 180 ml of chloroform, and the solution was irradiated with sunlight for 24 hours. After careful concentration of the reaction mixture, methanol was added thereto and deposited crystals were collected by filtration. The crystals were dried under reduced pressure to give 1.72 g (yield 86%) of a mixture of Compound 47 and Compound 1 as a pale yellow powder (The ratio of Compound 47 to Compound 1 was about 6 : 4 by NMR analysis).
Melting Point: 115.2-119.4 • C

Elemental Analysis: $C_{22}H_{28}N_4O_4$			
Calcd. (%):	C, 64.06;	H, 6.84;	N, 13.58
Found (%):	C, 64.02;	H, 6.82;	N, 13.46

IR (KBr) ν_{max} (cm^{-1}): 1695, 1656, 1521

NMR (DMSO-d_6; 270MHz) δ (ppm): 7.60(1x4/10H, d, J=15.8Hz), 7.40(1x4/10H, d, J=2.0Hz), 7.32-7.17 (2x4/10H + 2x6/10H, m), 6.99(1x4/10H, d, J=8.4Hz), 6.94-(1x6/10H, d, J=12.7Hz), 6.92(1x6/10H, d, J=8.2Hz), 6.39-(1x6/10H, d, J=12.7Hz), 4.02 (3x4/10H, s), 4.10-3.80(4H, m), 3.85(3x4/10H, s), 3.80(3x4/10H, s), 3.77(6x6/10H, s), 3.64-(3x6/10H, s), 1.80-1.55(4H, m), 1.00-0.85(6H, m)

Reference Example 45

(E)-8-(4-Ethoxystyryl)-1,3-dipropylxanthine (Compound 48)

Substantially the same procedure as in Reference Example 1 was repeated using 3.0 g (13.3 mmol) of 5,6-diamino-1,3-dipropyluracil and 2.80 g (14.6 mmol) of 4-ethoxycinnamic acid. Then, the resultant crude crystals were recrystallized from dioxane to give 3.57 g (yield 70%) of Compound 48 as pale yellow needles.

Melting Point: 261.6-262.0 °C

Elemental Analysis: $C_{21}H_{26}N_4O_3$			
Calcd. (%):	C, 65.96;	H, 6.85;	N, 14.65
Found (%):	C, 65.93;	H, 7.13;	N, 14.65

IR (KBr) ν_{max} (cm^{-1}): 1701, 1635, 1516, 1261

NMR (DMSO-d_6; 270MHz) δ (ppm): 13.37(1H, brs), 7.59 (1H, d, J=16.5Hz), 7.55(2H, d, J=8.6Hz), 6.96(2H, d, J=8.6Hz), 6.88(1H, d, J=16.5Hz), 4.07(2H, q, J=6.9Hz), 3.99(2H, t, J=7.3Hz), 3.86(2H, t, J=7.3Hz), 1.73(2H, m), 1.58(2H, m), 1.34(3H, t, J=6.9Hz), 0.90(3H, t, J=7.3Hz), 0.87(3H, t, J=7.3Hz)

Reference Example 46

(E)-8-(4-Ethoxystyryl)-7-methyl-1,3-dipropylxanthine (Compound 49)

Substantially the same procedure as in Reference Example 1 was repeated using 2.0 g (5.23 mmol) of Compound 48 obtained in Reference Example 45 in place of Compound B. Then, the resultant crude crystals were recrystallized from hexane/ethyl acetate to give 1.72 g (yield 83%) of Compound 49 as pale green needles.

Melting Point: 174.7-175.0 °C

Elemental Analysis: $C_{22}H_{28}N_4O_3$			
Calcd. (%):	C, 66.65;	H, 7.11;	N, 14.13
Found (%):	C, 66.60;	H, 7.20;	N, 14.27

IR (KBr) ν_{max} (cm^{-1}): 1702, 1660, 1515, 1252

NMR ($CDCl_3$; 270MHz) δ (ppm): 7.74(1H, d, J=15.8Hz), 7.52(2H, d, J=8.6Hz), 6.92(2H, d, J=8.6Hz), 6.76 (1H, d, J=15.8Hz), 4.09(2H, t, J=7.6Hz), 4.08(2H, q, J=6.9Hz), 4.04(3H, s), 3.99(2H, t, J=7.6Hz), 1.44(3H, t, J=6.9Hz), 1.00(3H, t, J=7.6Hz), 0.97 (3H, t, J=7.6Hz)

Reference Example 47

(E)-8-(4-Propoxystyryl)-1,3-dipropylxanthine (Compound 50)

Substantially the same procedure as in Reference Example 1 was repeated using 3.0 g (13.3 mmol) of 5,6-diamino-1,3-dipropyluracil and 3.01 g (14.6 mmol) of 4-propoxycinnamic acid. Then, the resultant crude crystals were recrystallized from dioxane/water to give 1.71 g (yield 33%) of Compound 50 as pale brown needles.

Melting Point: 248.3-248.7 • C

Elemental Analysis: $C_{22}H_{28}N_4O_3$			
Calcd. (%):	C, 66.65;	H, 7.11;	N, 14.13
Found (%):	C, 66.50;	H, 7.48;	N, 14.25

IR (KBr) ν_{max} (cm^{-1}): 1694, 1649, 1514, 1253

NMR (DMSO-d_6; 270MHz) δ (ppm): 13.34(1H, brs), 7.58 (1H, d, J = 16.5Hz), 7.55(2H, d, J = 8.6Hz), 6.99(2H, d, J = 8.6Hz), 6.88(1H, d, J = 16.5Hz), 4.01-3.95(4H, m), 3.86(2H, t, J = 7.3Hz), 1.78-1.70(4H, m), 1.62-1.54(2H, m), 0.98-(3H, t, J = 7.3Hz), 0.90(3H, t, J = 7.6Hz), 0.87(3H, t, J = 7.6Hz)

Reference Example 48

(E)-7-Methyl-8-(4-propoxystyryl)-1,3-dipropylxanthine (Compound 51)

Substantially the same procedure as in Reference Example 1 was repeated using 1.0 g (2.52 mmol) of Compound 50 obtained in Reference Example 47 in place of Compound B. Then, the resultant crude crystals were recrystallized from hexane/ethyl acetate to give 863 mg (yield 83%) of Compound 51 as pale yellow needles.

Melting Point: 172.6-173.5 • C

Elemental Analysis: $C_{23}H_{30}N_4O_3$			
Calcd. (%):	C, 67.30;	H, 7.36;	N, 13.65
Found (%):	C, 67.15;	H, 7.65;	N, 13.58

IR (KBr) ν_{max} (cm^{-1}): 1699, 1658, 1514, 1252

NMR ($CDCl_3$; 270MHz) δ (ppm): 7.74(1H, d, J = 15.8Hz), 7.52(2H, d, J = 8.9Hz), 6.92(2H, d, J = 8.9Hz), 6.76 (1H, d, J = 15.8Hz), 4.13-3.94(6H, m), 4.04(3H, s), 1.90-1.62(6H, m), 1.08-0.94(9H, m)

Reference Example 49

(E)-8-(4-Butoxystyryl)-1,3-dipropylxanthine (Compound 52)

Substantially the same procedure as in Reference Example 1 was repeated using 3.0 g (13.3 mmol) of 5,6-diamino-1,3-dipropyluracil and 3.21 g (14.6 mmol) of 4-butoxycinnamic acid. Then, the resultant crude crystals were recrystallized from dioxane/water to give 3.47 g (yield 64%) of Compound 52 as white needles.

Melting Point: 237.3-238.9 • C

Elemental Analysis: $C_{23}H_{30}N_4O_3$			
Calcd. (%):	C, 67.30;	H, 7.36;	N, 13.65
Found (%):	C, 67.39;	H, 7.45;	N, 13.59

IR (KBr) ν_{max} (cm^{-1}): 1697, 1644, 1514, 1257

NMR (DMSO-d_6; 270MHz) δ (ppm): 13.37(1H, brs), 7.58 (1H, d, J=16.2Hz), 7.55(2H, d, J=8.6Hz), 6.97(2H, d, J=8.6Hz), 6.88(1H, d, J=16.2Hz), 4.04-3.96(4H, m), 3.86(2H, t, J=7.3Hz), 1.80-1.37(8H, m), 0.97-0.84(9H, m)

Reference Example 50

(E)-8-(4-Butoxystyryl)-7-methyl-1,3-dipropylxanthine (Compound 53)

Substantially the same procedure as in Reference Example 1 was repeated using 2.0 g (4.87 mmol) of Compound 52 obtained in Reference Example 49 in place of Compound B. Then, the resultant crude crystals were recrystallized from hexane/ethyl acetate to give 1.56 g (yield 75%) of Compound 53 as pale green needles.

Melting Point: 134.8-135.6 • C

Elemental Analysis: $C_{24}H_{32}N_4O_3$			
Calcd. (%):	C, 67.90;	H, 7.59;	N, 13.20
Found (%):	C, 68.22;	H, 7.88;	N, 13.49

IR (KBr) ν_{max} (cm^{-1}): 1696, 1651, 1513, 1247

NMR ($CDCl_3$; 270MHz) δ (ppm): 7.74(1H, d, J=15.5Hz), 7.52(2H, d, J=8.6Hz), 6.92(2H, d, J=8.6Hz), 6.76 (1H, d, J=15.5Hz), 4.13-3.95(6H, m), 4.04(3H, s), 1.88-1.44(8H, m), 1.03-0.94(9H, m)

Reference Example 51

(E)-8-(3,4-Dihydroxystyryl)-7-methyl-1,3-dipropylxanthine (Compound 54)

Compound 1 (770 mg, 1.87 mmol) obtained in Reference Example 1 was dissolved in 15 ml of methylene chloride. To the solution was added 5.6 ml (5.6 mmol) of boron tribromide (1.0M methylene chloride solution) under ice cooling in argon atmosphere, and the mixture was stirred overnight at room temperature. Methanol was added thereto and the mixture was separated with chloroform-an aqueous solution of sodium bicarbonate. The organic layer was washed with a saturated aqueous solution of sodium chloride and dried over anhydrous sodium sulfate, followed by evaporation under reduced pressure. The residue was purified by silica gel column chromatography to give 550 mg (yield 77%) of Compound 54 as a yellow solid, which was then triturated with ether to give a yellow powder.

Melting Point: 250.1-251.4 • C

Elemental Analysis: $C_{20}H_{24}N_4O_4$			
Calcd. (%):	C, 62.49;	H, 6.29;	N, 14.57
Found (%):	C, 62.27;	H, 6.48;	N, 14.74

IR (KBr) ν_{max} (cm^{-1}): 1680, 1640, 1543, 1306

NMR (DMSO-d_6; 270MHz) δ (ppm): 9.31(1H, brs), 8.95(1H, brs), 7.49(1H, d, J=15.8Hz), 7.15(1H, d, J=2.0Hz), 7.04(1H, dd, J=7.9, 2.0Hz), 6.98(1H, d, J=15.8Hz), 6.78(1H, d, J=7.9Hz), 3.99(2H, t, J=7.6Hz), 3.98 (3H, s), 3.84-(2H, t, J=7.4Hz), 1.73(2H, m), 1.57 (2H, m), 0.90(3H, t, J=7.4Hz), 0.87(3H, t, J=7.4Hz)

Reference Example 52

(E)-8-(3,4-Diethoxystyryl)-7-methyl-1,3-dipropylxanthine (Compound 55)

Compound 54 (390 mg, 1.01 mmol) obtained in Reference Example 51 was dissolved in 10 ml of dimethylformamide. To the solution were added 0.20 ml (2.50 mmol) of ethyl iodide and 420 mg (3.04 mmol) of potassium carbonate, and the mixture was stirred overnight at room temperature. Water was added thereto to dissolve potassium carbonate and deposited crystals were collected by filtration. The collected crude crystals were recrystallized from hexane/ethyl acetate to give 237 mg (yield 53%) of Compound 55 as pale yellow needles.

Melting Point: 173.8-174.0 °C

Elemental Analysis: $C_{24}H_{32}N_4O_4$			
Calcd. (%):	C, 65.44;	H, 7.32;	N, 12.72
Found (%):	C, 65.42;	H, 7.48;	N, 12.62

IR (KBr) ν_{max} (cm^{-1}): 1694, 1653, 1508, 1268

NMR ($CDCl_3$; 270MHz) δ (ppm): 7.71(1H, d, J=15.5Hz), 7.15(1H, dd, J=8.3, 2.0Hz), 7.10(1H, d, J=2.0Hz), 6.89(1H, d, J=8.3Hz), 6.74(1H, d, J=15.5Hz), 4.16 (2H, q, J=6.9Hz), 4.14(2H, q, J=6.9Hz), 4.08-3.95 (4H, m), 4.05(3H, s), 1.91-1.76(2H, m), 1.76-1.62 (2H, m), 1.49(3H, t, J=6.9Hz), 1.48(3H, t, J=6.9Hz), 1.00(3H, t, J=7.6Hz), 0.97(3H, t, J=7.6Hz)

Reference Example 53

(E)-8-(3-Bromo-4-methoxystyryl)-1,3-dipropylxanthine (Compound 56)

Substantially the same procedure as in Reference Example 1 was repeated using 3.0 g (13.3 mmol) of 5,6-diamino-1,3-dipropyluracil and 3.75 g (14.6 mmol) of 3-bromo-4-methoxycinnamic acid. Then, the resultant crude crystals were recrystallized from dioxane to give 3.43 g (yield 58%) of Compound 56 as yellow needles.

Melting Point: 279.8-280.6 °C

Elemental Analysis: $C_{20}H_{23}N_4O_3Br$			
Calcd. (%):	C, 53.70;	H, 5.18;	N, 12.52
Found (%):	C, 53.77;	H, 5.20;	N, 12.49

IR (KBr) ν_{max} (cm^{-1}): 1685, 1633, 1599, 1503, 1279

NMR (DMSO-d_6; 270MHz) δ (ppm): 13.42(1H, brs), 7.85 (1H, d, J=2.0Hz), 7.61(1H, dd, J=8.4, 2.0Hz), 7.55 (1H, d, J=16.3Hz), 7.15(1H, d, J=8.4Hz), 6.94(1H, d, J=16.3Hz), 3.98(2H, t, J=7.4Hz), 3.89(3H, s), 3.86(2H, t, J=7.4Hz), 1.80-1.52(4H, m), 0.89(6H, q, J=7.4Hz)

Reference Example 54

(E)-8-(3-Bromo-4-methoxystyryl)-7-methyl-1,3-dipropylxanthine (Compound 57)

Substantially the same procedure as in Reference Example 1 was repeated using 750 mg (1.68 mmol) of Compound 56 obtained in Reference Example 53 in place of Compound B. Then, the resultant crude crystals were recrystallized from hexane/ethyl acetate to give 588 mg (yield 76%) of Compound 57 as pale yellow needles.

Melting Point: 209.4-210.8 °C

Elemental Analysis: $C_{21}H_{25}N_4O_3Br$			
Calcd. (%):	C, 54.67;	H, 5.46;	N, 12.14
Found (%):	C, 54.47;	H, 5.51;	N, 11.91

IR (KBr) ν_{max} (cm^{-1}): 1693, 1656, 1542, 1500, 1264

NMR ($CDCl_3$; 270MHz) δ (ppm): 7.83(1H, d, J=2.0Hz), 7.68(1H, d, J=15.8Hz), 7.48(1H, dd, J=8.4, 2.0Hz), 6.92(1H, d, J=8.4Hz), 6.78(1H, d, J=15.8Hz), 4.13-4.07(2H, m), 4.06(3H, s), 4.01-3.97(2H, m), 3.95 (3H, s), 1.90-1.65(4H, m), 1.00(3H, t, J=7.4Hz), 0.97(3H, t, J=7.4Hz)

Reference Example 55

(E)-8-(2-Bromo-4,5-dimethoxystyryl)-1,3-dipropylxanthine (Compound 58)

Substantially the same procedure as in Reference Example 1 was repeated using 2.0 g (8.85 mmol) of 5,6-diamino-1,3-dipropyluracil and 2.80 g (9.75 mmol) of 2-bromo-4,5-dimethoxycinnamic acid. Then, the resultant crude crystals were recrystallized from dioxane to give 2.38 g (yield 56%) of Compound 58 as pale yellow needles.

Melting Point: 248.2-249.5 °C

Elemental Analysis: $C_{21}H_{25}N_4O_4Br$			
Calcd. (%):	C, 52.84;	H, 5.28;	N, 11.74
Found (%):	C, 52.73;	H, 5.31;	N, 11.45

IR (KBr) ν_{max} (cm^{-1}): 1697, 1643, 1506, 1263

NMR (DMSO-d_6; 270MHz) δ (ppm): 13.75(1H, brs), 7.81 (1H, d, J=16.3Hz), 7.39(1H, s), 7.20(1H, s), 7.09 (1H, d, J=16.3Hz), 4.00-3.82(4H, m), 3.86(3H, s), 3.82(3H, s), 1.76-1.54(4H, m), 0.92-0.85(6H, m)

Reference Example 56

(E)-8-(2-Bromo-4,5-dimethoxystyryl)-7-methyl-1,3-dipropylxanthine (Compound 59)

Substantially the same procedure as in Reference Example 1 was repeated using 800 mg (1.68 mmol) of Compound 58 obtained in Reference Example 55 in place of Compound B. Then, the resultant crude crystals were recrystallized from dioxane to give 766 mg (yield 93%) of Compound 59 as yellow needles.

Melting Point: 228.8-229.4 °C

Elemental Analysis: $C_{22}H_{27}N_4O_4Br$			
Calcd. (%):	C, 53.78;	H, 5.54;	N, 11.40
Found (%):	C, 53.76;	H, 5.67;	N, 11.16

IR (KBr) ν_{max} (cm^{-1}): 1688, 1650, 1509, 1266

NMR ($CDCl_3$; 270MHz) δ (ppm): 8.01(1H, d, J=15.8Hz), 7.11(1H, s), 7.09(1H, s), 6.75(1H, d, J=15.8Hz), 4.15-3.92(4H, m), 4.08(3H, s), 3.95(3H, s), 3.92 (3H, s), 1.91-1.77(2H, m), 1.74-1.63(2H, m), 1.03-0.94(6H, m)

Reference Example 57

(E)-8-(3-Bromo-4,5-dimethoxystyryl)-1,3-dipropylxanthine (Compound 60)

Substantially the same procedure as in Reference Example 1 was repeated using 1.5 g (6.64 mmol) of 5,6-diamino-1,3-dipropyluracil and 2.10 g (7.31 mmol) of 3-bromo-4,5-dimethoxycinnamic acid. Then, the resultant crude crystals were recrystallized from dioxane/water to give 2.11 g (yield 67%) of Compound 60

as white needles.

Melting Point: 276.7-277.5 °C

Elemental Analysis: $C_{21}H_{25}N_4O_4Br$			
Calcd. (%):	C, 52.84;	H, 5.28;	N, 11.74
Found (%):	C, 52.72;	H, 5.16;	N, 11.56

IR (KBr) ν_{max} (cm^{-1}): 1701, 1650, 1562, 1498

NMR (DMSO-d_6; 270MHz) δ (ppm): 13.44(1H, brs), 7.55 (1H, d, J=16.3Hz), 7.39(1H, d, J=2.0Hz), 7.36(1H, d, J=2.0Hz), 7.07(1H, d, J=16.3Hz), 3.99(2H, t, J=7.4Hz), 3.91(3H, s), 3.86(2H, t, J=7.4Hz), 3.78 (3H, s), 1.77-1.52(4H, m), 0.93-0.85(6H, m)

Reference Example 58

(E)-8-(3-Bromo-4,5-dimethoxystyryl)-7-methyl-1,3-dipropylxanthine (Compound 61)

Substantially the same procedure as in Reference Example 1 was repeated using 1.0 g (2.10 mmol) of Compound 60 obtained in Reference Example 57 in place of Compound B. Then, the resultant crude crystals were recrystallized from hexane/ethyl acetate to give 952 mg (yield 93%) of Compound 61 as pale yellow needles.

Melting Point: 180.9-181.6 °C

MS-EI m/e: 490, 492

IR (KBr) ν_{max} (cm^{-1}): 1691, 1648, 1542, 1493

NMR ($CDCl_3$; 270MHz) δ (ppm): 7.68(1H, d, J=15.8Hz), 7.42(1H, d, J=2.0Hz), 7.02(1H, d, J=2.0Hz), 6.80 (1H, d, J=15.8Hz), 4.13-3.95(4H, m), 4.08(3H, s), 3.94(3H, s), 3.90(3H, s), 1.90-1.65(4H, m), 1.01 (3H, t, J=7.4Hz), 0.97(3H, t, J=7.4Hz)

Reference Example 59

(E)-8-[2-(4-Methoxynaphthyl)vinyl]-1,3-dipropylxanthine(Compound 62)

Substantially the same procedure as in Reference Example 1 was repeated using 3.0 g (13.3 mmol) of 5,6-diamino-1,3-dipropyluracil and 3.33 g (14.6 mmol) of 3-(4-methoxynaphthyl)acrylic acid. Then, the resultant crude crystals were recrystallized from dioxane/water to give 3.12 g (yield 56%) of Compound 62 as yellow needles.

Melting Point: >280 °C

Elemental Analysis: $C_{24}H_{26}N_4O_3$			
Calcd. (%):	C, 68.88;	H, 6.26;	N, 13.39
Found (%):	C, 68.90;	H, 6.38;	N, 13.49

IR (KBr) ν_{max} (cm^{-1}): 1699, 1649, 1486, 1273

NMR (DMSO-d_6; 270MHz) δ (ppm): 13.58(1H, brs), 8.43 (1H, d, J=16.5Hz), 8.36(1H, d, J=8.6Hz), 8.24(1H, d, J=8.6Hz), 7.98(1H, d, J=7.8Hz), 7.70-7.54(2H, m), 7.12-7.06(2H, m), 4.03(3H, s), 4.02-3.86(4H, m), 1.79-1.56(4H, m), 0.92(3H, s), 0.89(3H, s)

Reference Example 60

(E)-8-[2-(4-Methoxynaphthyl)vinyl]-7-methyl-1,3-dipropylxanthine (Compound 63)

Substantially the same procedure as in Reference Example 1 was repeated using 1.6 g (3.82 mmol) of Compound 62 obtained in Reference Example 59 in place of Compound B. Then, the resultant crude

crystals were recrystallized from ethyl acetate to give 1.25 g (yield 76%) of Compound 63 as pale yellow plates.

Melting Point: 212.6-213.9 °C

Elemental Analysis: $C_{25}H_{28}N_4O_3$			
Calcd. (%):	C, 69.43;	H, 6.52;	N, 12.95
Found (%):	C, 69.46;	H, 6.68;	N, 12.95

IR (KBr) ν_{max} (cm^{-1}): 1701, 1650, 1486, 1439, 1267

NMR ($CDCl_3$; 270MHz) δ (ppm): 8.52(1H, d, J=15.5Hz), 8.34(1H, d, J=8.3Hz), 8.23(1H, d, J=8.6Hz), 7.77 (1H, d, J=8.3Hz), 7.66-7.52(2H, m), 6.89(1H, d, J=15.5Hz), 6.87(1H, d, J=8.3Hz), 4.18-4.11(2H, m), 4.07(3H, s), 4.06(3H, s), 4.02-3.97(2H, m), 1.95-1.64(4H, m), 1.03(3H, t, J=7.3Hz), 0.98(3H, t, J=7.3Hz)

Reference Example 61

(E)-8-(3-Hydroxy-4-methoxystyryl)-7-methyl-1,3-dipropylxanthine (Compound 64)

Compound 54 (500 mg, 1.30 mmol) obtained in Reference Example 51 was dissolved in 10 ml of dimethylformamide. To the solution were added 0.40 ml (6.43 mmol) of methyl iodide and 400 mg (6.50 mmol) of lithium carbonate, and the mixture was stirred at 80 °C for 5 hours. Water was added thereto to dissolve lithium carbonate and deposited crystals were collected by filtration. The collected crude crystals were dissolved in chloroform, washed with a saturated aqueous solution of sodium chloride and dried over anhydrous sodium sulfate, followed by evaporation under reduced pressure. The residue was purified by silica gel column chromatography (eluent: chloroform), followed by recrystallization from hexane/ethyl acetate to give 162 mg (yield 31%) of Compound 64 as yellow grains.

Melting Point: 200.3-203.6 °C

MS-EI m/e: 398

IR (KBr) ν_{max} (cm^{-1}): 1683, 1642, 1512, 1278

NMR (DMSO-d_6; 270MHz) δ (ppm): 8.98(1H, brs), 7.52(1H, d, J=15.5Hz), 7.22(1H, d, J=2.0Hz), 7.15-(1H, dd, J=8.3, 2.0Hz), 7.06(1H, d, J=15.5Hz), 6.96 (1H, d, J=8.3Hz), 4.02-3.97(2H, m), 4.00(3H, s), 3.84-3.82 (2H, m), 3.82-(3H, s), 1.80-1.50 (4H, m), 0.90(3H, t, J=7.3Hz), 0.87(3H, t, J=7.3Hz)

Reference Example 62

(Z)-8-(3,4-Dimethoxystyryl)-7-methyl-1,3-dipropylxanthine (Compound 65)

Compound 1 (1.00 g, 2.42 mmol) obtained in Reference Example 1 was dissolved in 1.6 L of methanol, and the solution was irradiated with sunlight for 5 hours. After evaporation under reduced pressure, the residue was purified by high performance liquid chromatography (column: YMC Pack ODS-A, SH-365-10, S-10; 30 mmø x 500 mm, flow rate: 90 ml/min, detection: UV 246 nm) to give 565 mg (yield 57%) of Compound 65 as white needles.

Melting Point: 126.9-127.2 °C

Elemental Analysis: $C_{22}H_{28}N_4O_4$			
Calcd. (%):	C, 64.06;	H, 6.84;	N, 13.58
Found (%):	C, 64.12;	H, 7.09;	N, 13.54

IR (KBr) ν_{max} (cm^{-1}): 1696, 1654, 1542, 1521

NMR (270MHz; DMSO-d_6) δ (ppm): 7.28(1H, d, J=8.4Hz), 7.20(1H, s), 6.94(1H, d, J=12.7Hz), 6.92-(1H, d, J=8.4Hz), 6.39(1H, d, J=12.7Hz), 3.93(2H, t, J=7.4Hz), 3.84(2H, t, J=6.9Hz), 3.77(6H, s), 3.64 (3H, s), 1.75-1.50(4H, m), 0.86(3H, t, J=7.4Hz), 0.85(3H, t, J=7.4Hz)

Reference Example 63

(E)-8-(3,4-Dimethoxystyryl)-7-ethyl-1,3-dipropylxanthine (Compound 66)

Substantially the same procedure as in Reference Example 1 was repeated using 1.5 g (3.77 mmol) of Compound B obtained in Reference Example 1 and 0.60 ml (7.54 mmol) of ethyl iodide. Then, the resultant crude crystals were recrystallized from ethanol/water to give 1.38 g (yield 87%) of Compound 66 as white needles.

Melting Point: 107.6-107.9 °C

Elemental Analysis: $C_{23}H_{30}N_4O_4$			
Calcd. (%):	C, 64.77;	H, 7.09;	N, 13.14
Found (%):	C, 64.81;	H, 7.28;	N, 13.21

IR (KBr) ν_{max} (cm^{-1}): 1695, 1655, 1515, 1265

NMR (270MHz; $CDCl_3$) δ (ppm): 7.63(1H, d, J=15.8Hz), 7.42(1H, d, J=1.7Hz), 7.32(1H, dd, J=8.6, 1.7Hz), 7.23(1H, d, J=15.8Hz), 6.99(1H, d, J=8.6Hz), 4.51 (2H, q, J=6.9Hz), 3.99(2H, t, J=7.2Hz), 3.87-3.80 (2H, m), 3.85(3H, s), 3.80-(3H, s), 1.80-1.45(4H, m), 1.33(3H, t, J=6.9Hz), 0.94-0.85(6H, m)

Reference Example 64

(E)-8-(3,4-Dimethoxystyryl)-7-propargyl-1,3-dipropylxanthine (Compound 67)

Substantially the same procedure as in Reference Example 1 was repeated using 1.5 g (3.77 mmol) of Compound B obtained in Reference Example 1 and 0.67 ml (7.54 mmol) of propargyl bromide. Then, the resultant crude crystals were recrystallized from cyclohexane/toluene to give 1.35 g (yield 82%) of Compound 67 as a yellow powder.

Melting Point: 153.4-154.8 °C

Elemental Analysis: $C_{24}H_{28}N_4O_4$			
Calcd. (%):	C, 66.04;	H, 6.47;	N, 12.84
Found (%):	C, 66.18;	H, 6.74;	N, 12.87

IR (KBr) ν_{max} (cm^{-1}): 1684, 1647, 1510, 1270

NMR (270MHz; $CDCl_3$) δ (ppm): 7.66(1H, d, J=15.7Hz), 7.41(1H, d, J=1.3Hz), 7.32(1H, dd, J=8.5, 1.3Hz), 7.26(1H, d, J=15.7Hz), 7.02(1H, d, J=8.5Hz), 5.43 (2H, d, J=2.0Hz), 4.00(2H, t, J=7.3Hz), 3.87-3.81 (2H, m), 3.85(3H, s), 3.81-(3H, s), 3.48(1H, t, J=2.0Hz), 1.80-1.45(4H, m), 0.94-0.85(6H, m)

Reference Example 65

(E)-8-[3,4-Bis(methoxymethoxy)styryl]-7-methyl-1,3-dipropylxanthine (Compound 68)

Compound 54 (300 mg, 0.78 mmol) obtained in Reference Example 51 was dissolved in 6 ml of tetrahydrofuran. To the solution were added 1.64 ml (9.41 mmol) of diisopropylethylamine and 1.64 ml (7.12 mmol) of chloromethylmethyl ether under ice-cooling in a stream of argon, and the mixture was heated under reflux for 3 hours. Ice was added to the reaction solution and the mixture was separated with chloroform-a saturated aqueous saline solution. The organic layer was dried over anhydrous sodium sulfate, followed by evaporation under reduced pressure. The residue was purified by silica gel column chromatography (eluent: hexane/ethyl acetate) and recrystallized from hexane/ethyl acetate to give 211 mg (yield 57%) of Compound 68 as white needles.

Melting Point: 172.2-172.6 °C

Elemental Analysis: $C_{24}H_{32}N_4O_6$			
Calcd. (%):	C, 61.01;	H, 6.82;	N, 11.86
Found (%):	C, 61.16;	H, 7.00;	N, 11.88

IR (KBr) ν_{max} (cm^{-1}): 1688, 1658, 1509, 1267

NMR (270MHz; $CDCl_3$) δ (ppm): 7.22(1H, d, J=15.8Hz), 7.39(1H, d, J=1.3Hz), 7.25-7.16(2H, m), 6.77(1H, d, J=15.8Hz), 5.30(2H, s), 5.28(2H, s), 4.13-3.95 (4H, m), 4.04(3H, s), 3.56(3H, s), 3.54(3H, s), 1.91-1.61(4H, m), 1.00(3H, t, J=7.6Hz), 0.97(3H, t, J=7.6Hz)

Reference Example 66

(E)-1,3-Diallyl-8-(3,4-dimethoxystyryl)xanthine (Compound 69)

Substantially the same procedure as in Reference Example 1 was repeated using 2.9 g (13.1 mmol) of 1,3-diallyl-5,6-diaminouraciland 2.99 g (14.4 mmol) of 3,4-dimethoxycinnamic acid. Then, the resultant crude crystals were recrystallized from dioxane/water to give 2.80 g (yield 54%) of Compound 69 as pale yellow flocculent precipitates.

Melting Point: 251.6-252.4 °C

Elemental Analysis: $C_{21}H_{22}N_4O_3$			
Calcd. (%):	C, 63.95;	H, 5.62;	N, 14.20
Found (%):	C, 63.67;	H, 5.61;	N, 14.14

IR (KBr) ν_{max} (cm^{-1}): 1698, 1644, 1516

NMR (270MHz; DMSO-d_6) δ (ppm): 13.50(1H, brs), 7.58 (1H, d, J=16.3Hz), 7.27(1H, d, J=2.0Hz), 7.13(1H, dd, J=8.4, 2.0Hz), 6.99(1H, d, J=8.4Hz), 6.96(1H, d, J=16.3Hz), 6.07-5.82(2H, m), 5.20-5.01(4H, m), 4.68-4.45(4H, m), 3.82(3H, s), 3.79(3H, s)

Reference Example 67

(E)-1,3-Diallyl-8-(3,4-dimethoxystyryl)-7-methylxanthine (Compound 70)

Substantially the same procedure as in Reference Example 1 was repeated using 2.30 g (5.84 mmol) of Compound 69 obtained in Reference Example 66 in place of Compound B. Then, the resultant crude crystals were recrystallized from ethanol to give 1.85 g (yield 78%) of Compound 70 as pale yellow flocculent precipitates.

Melting Point: 159.5-160.0 °C

Elemental Analysis: $C_{22}H_{24}N_4O_3$			
Calcd. (%):	C, 64.69;	H, 5.92;	N, 13.72
Found (%):	C, 64.50;	H, 6.03;	N, 13.71

IR (KBr) ν_{max} (cm^{-1}): 1698, 1658, 1515, 1265

NMR (270MHz; DMSO-d_6) δ (ppm): 7.60(1H, d, J=15.3Hz), 7.42(1H, d, J=1.5Hz), 7.29(1H, dd, J=8.4, 1.5Hz), 7.21(1H, d, J=15.3Hz), 6.99(1H, d, J=8.4Hz), 6.05-5.78(2H, m), 5.20-5.01(4H, m), 4.68-4.45(4H, m), 4.03(3H, s); 3.84(3H, s), 3.80(3H, s)

Reference Example 68

(E)-8-(3,4-Dimethoxystyryl)-1,3-dipropyl-2-thioxanthine(Compound 71)

Substantially the same procedure as in Reference Example 1 was repeated using 4.00 g (16.5 mmol) of 5,6-diamino-1,3-dipropyl-2-thiouracil and 3.79 g (18.2 mmol) of 3,4-dimethoxycinnamic acid. Then, the resultant crude crystals were recrystallized from dioxane/water to give 3.16 g (yield 46%) of Compound 71 as yellow needles.

Melting Point: 273.2-272.4 °C

Elemental Analysis: $C_{21}H_{26}N_4O_3S$			
Calcd. (%):	C, 60.85;	H, 6.32;	N, 13.52
Found (%):	C, 60.85;	H, 6.49;	N, 13.64

IR (KBr) ν_{max} (cm^{-1}): 1675, 1515

NMR (270MHz; DMSO-d_6) δ (ppm): 7.64(1H, d, J=16.5Hz), 7.30(1H, s), 7.15(1H, d, J=8.2Hz), 7.02-(1H, d, J=16.5Hz), 6.99(1H, d, J=8.2Hz), 4.56(2H, t, J=7.6Hz), 4.45(2H, t, J=7.6Hz), 3.83(3H, s), 3.80 (3H, s), 1.85-1.60(4H, m), 0.98-0.82(6H, m)

Reference Example 69

(E)-8-(3,4-Dimethoxystyryl)-7-methyl-1,3-dipropyl-2-thioxanthine (Compound 72)

Substantially the same procedure as in Reference Example 1 was repeated using 3.00 g (7.25 mmol) of Compound 71 obtained in Reference Example 68 in place of Compound B. Then, the resultant crude crystals were recrystallized from toluene/ethanol to give 1.79 g (yield 58%) of Compound 72 as a pale yellow powder.

Melting Point: 137.3-139.2 °C

Elemental Analysis: $C_{22}H_{28}N_4O_3S$			
Calcd. (%):	C, 61.66;	H, 6.59;	N, 13.07
Found (%):	C, 61.44;	H, 6.71;	N, 13.05

IR (KBr) ν_{max} (cm^{-1}): 1684, 1515, 1438

NMR (270MHz; DMSO-d_6) δ (ppm): 7.67(1H, d, J=15.7Hz), 7.44(1H, d, J=1.3Hz), 7.33(1H, dd, J=8.3, 1.3Hz), 7.24(1H, d, J=15.7Hz), 7.00(1H, d, J=8.3Hz), 4.56 (2H, t, J=7.6Hz), 4.42(2H, t, J=7.6Hz), 4.06(3H, s), 3.85(3H, s), 3.81(3H, s), 1.85-1.60(4H, m), 0.98-0.82(6H, m)

Reference Example 70

(E)-8-(3,4-Dimethoxystyryl)-1,3-diethylxanthine (Compound 73)

3,4-Dimethoxycinnamic acid (1.39 g, 6.67 mmol) and 3-(3-diethylaminopropyl)-1-ethylcarbodiimide hydrochloride (1.74 g, 9.09 mmol) were added to a mixture of dioxane (40 ml) and water (20 ml) containing 5,6-diamino-1,3-diethyluracil [J. Am. Chem. Soc., 75, 114 (1953)] (1.20 g, 6.06 mmol). The resultant solution was stirred at room temperature for 2 hours at pH 5.5. After neutralization, the reaction solution was extracted three times with 50 ml of chloroform. The combined extract was washed with a saturated aqueous solution of sodium chloride and dried over anhydrous sodium sulfate, followed by evaporation under reduced pressure.

To the residue were added 10 ml of dioxane and 15 ml of an aqueous 1N sodium hydroxide solution, followed by heating under reflux for 20 minutes. After cooling, the solution was neutralized and 20 ml of chloroform was added thereto. The organic layer was separated and the aqueous layer was extracted twice with 20 ml of chloroform. The combined extract was washed with a saturated aqueous solution of sodium chloride and dried over anhydrous sodium sulfate, followed by evaporation under reduced pressure. The residue was purified by silica gel column chromatography (eluent: 2% methanol/chloroform), followed by recrystallization from toluene to give 1.06 g (yield 47%) of Compound 73 as pale yellow needles.

Melting Point: 268.8-269.1 °C

Elemental Analysis: $C_{19}H_{22}N_4O_4$			
Calcd. (%):	C, 61.61;	H, 5.98;	N, 15.12
Found (%):	C, 61.99;	H, 6.00;	N, 14.91

IR (KBr) ν_{max} (cm^{-1}): 1694, 1641, 1514, 1492

NMR (270MHz; DMSO-d_6) δ (ppm): 13.35(1H, brs), 7.59 (1H, d, J=16.2Hz), 7.27(1H, d, J=1.4Hz), 7.14(1H, dd, J=8.2, 1.4Hz), 6.99(1H, d, J=8.2Hz), 6.96(1H, d, J=16.2Hz), 4.06(2H, q, J=7.0Hz), 3.91(2H, q, J=7.0Hz), 3.83-(3H, s), 3.79(3H, s), 1.26(3H, t, J=7.0Hz), 1.14(3H, t, J=7.0Hz)

Reference Example 71

(E)-8-(3,4-Dimethoxystyryl)-1,3-diethyl-7-methylxanthine (Compound 74)

Substantially the same procedure as in Reference Example 1 was repeated using 1.20 g (3.24 mmol) of Compound 73 obtained in Reference Example 70 in place of Compound B. Then, the resultant crude crystals were purified by silica gel column chromatography (eluent: 40% ethyl acetate/hexane), followed by recrystallization from 2-propanol to give 840 mg (yield 68%) of Compound 74 as pale yellow needles.

Melting Point: 190.4-191.3 °C

Elemental Analysis: $C_{20}H_{24}N_4O_4$			
Calcd. (%):	C, 62.48;	H, 6.29;	N, 14.57
Found (%):	C, 62.52;	H, 6.53;	N, 14.56

IR (KBr) ν_{max} (cm^{-1}): 1697, 1655, 1518

NMR (270MHz; $CDCl_3$) δ (ppm): 7.74(1H, d, J=15.5Hz), 7.18(1H, dd, J=8.3, 1.9Hz), 7.08(1H, d, J=1.9Hz), 6.89(1H, d, J=8.3Hz), 6.77(1H, d, J=15.5Hz), 4.21 (2H, q, J=6.9Hz), 4.09(2H, q, J=6.9Hz), 4.06(3H, s), 3.96(3H, s), 3.93(3H, s), 1.39(3H, t, J=6.9Hz), 1.27(3H, t, J=6.9Hz)

Reference Example 72

(E)-8-(2,3-Dimethoxystyryl)-1,3-diethylxanthine (Compound 75)

Substantially the same procedure as in Reference Example 70 was repeated using 2.0 g (10.1 mmol) of 5,6-diamino-1,3-diethyluracil and 2.52 g (12.1 mmol) of 2,3-dimethoxycinnamic acid. Then, the resultant crude crystals were recrystallized from dimethylsulfoxide/water to give 1.72 g (yield 46%) of Compound 75 as a white powder.

Melting Point: 287.5-289.4 °C

Elemental Analysis: $C_{19}H_{22}N_4O_4$			
Calcd. (%):	C, 61.61;	H, 5.98;	N, 15.12
Found (%):	C, 61.56;	H, 6.11;	N, 14.83

IR (KBr) ν_{max} (cm^{-1}): 1697, 1656, 1500

NMR (270MHz; DMSO-d_6) δ (ppm): 13.64(1H, brs), 7.84 (1H, d, J=16.8Hz), 7.29(1H, dd, J=7.6, 1.7Hz), 7.15-7.00(3H, m), 4.07(2H, q, J=7.0Hz), 3.94(2H, q, J=7.0Hz), 3.83(3H, s), 3.79(3H, s), 1.26(3H, t, J=7.0Hz), 1.14(3H, t, J=7.0Hz)

Reference Example 73

(E)-8-(2,3-Dimethoxystyryl)-1,3-diethyl-7-methylxanthine (Compound 76)

Substantially the same procedure as in Reference Example 1 was repeated using 1.60 g (4.32 mmol) of Compound 75 obtained in Reference Example 72 in place of Compound B. Then, the resultant crude crystals were recrystallized from cyclohexane/toluene to give 1.21 g (yield 73%) of Compound 76 as a pale yellow powder.

Melting Point: 194.9-195.6 °C

Elemental Analysis: $C_{20}H_{24}N_4O_4$			
Calcd. (%):	C, 62.48;	H, 6.29;	N, 14.57
Found (%):	C, 62.67;	H, 6.48;	N, 14.31

IR (KBr) ν_{max} (cm^{-1}): 1694, 1660, 1272

NMR (270MHz; $CDCl_3$) δ (ppm): 8.00(1H, d, J=16.8Hz), 7.19(1H, dd, J=7.9, 1.3Hz), 7.15-7.00(2H, m), 6.93 (1H, dd, J=7.9, 1.3Hz), 4.26(2H, q, J=6.9Hz), 4.09 (2H, q, J=6.9Hz), 4.05(3H, s), 3.91(3H, s), 3.90 (3H, s), 1.39(3H, t, J=6.9Hz), 1.27(3H, t, J=6.9Hz)

Reference Example 74

(E)-8-(2,4-Dimethoxystyryl)-1,3-diethylxanthine (Compound 77)

Substantially the same procedure as in Reference Example 70 was repeated using 2.50 g (12.6 mmol) of 5,6-diamino-1,3-diethyluracil and 2.89 g (13.9 mmol) of 2,4-dimethoxycinnamic acid. Then, the resultant crude crystals were recrystallized from dimethylformamide/ethanol to give 0.92 g (yield 20%) of Compound 77 as yellow crystals.

Melting Point: 278.7-279.8 °C

Elemental Analysis: $C_{19}H_{22}N_4O_2$			
Calcd. (%):	C, 61.61;	H, 5.98;	N, 15.12
Found (%):	C, 61.65;	H, 5.95;	N, 14.74

IR (KBr) ν_{max} (cm^{-1}): 1698, 1640, 1509, 1292

NMR (270MHz; DMSO-d_6) δ (ppm): 13.43(1H, brs), 7.77 (1H, d, J=16.8Hz), 7.54(1H, d, J=8.4Hz), 6.95(1H, d, J=16.8Hz), 6.63(1H, d, J=2.5Hz), 6.60(1H, dd, J=8.4, 2.5Hz), 4.06(2H, q, J=6.9Hz), 3.93(2H, q, J=6.9Hz), 3.89-(3H, s), 3.82(3H, s), 1.25(3H, t, J=6.9Hz), 1.13(3H, t, J=6.9Hz)

Reference Example 75

(E)-8-(2,4-Dimethoxystyryl)-1,3-diethyl-7-methylxanthine (Compound 78)

Substantially the same procedure as in Reference Example 1 was repeated using 400 mg (1.08 mmol) of Compound 77 obtained in Reference Example 74 in place of Compound B. Then, the resultant crude crystals were recrystallized from hexane/ethyl acetate to give 335 mg (yield 81%) of Compound 78 as yellow needles.

Melting Point: 195.9-196.7 • C

Elemental Analysis: $C_{20}H_{24}N_4O_4$			
Calcd. (%):	C, 62.48;	H, 6.29;	N, 14.57
Found (%):	C, 62.29;	H, 6.51;	N, 14.66

IR (KBr) ν_{max} (cm^{-1}): 1693, 1654, 1603, 1294

NMR (270MHz; $CDCl_3$) δ (ppm): 7.93(1H, d, J=15.8Hz), 7.48(1H, d, J=8.3Hz), 6.97(1H, d, J=15.8Hz), 6.53 (1H, dd, J=8.3, 2.0Hz), 6.49(1H, d, J=2.0Hz), 4.22 (2H, q, J=6.9Hz), 4.08(2H, q, J=6.9Hz), 4.02(3H, s), 3.92(3H, s), 3.86(3H, s), 1.38(3H, t, J=6.9Hz), 1.26(3H, t, J=6.9Hz)

Reference Example 76

(E)-1,3-Diethyl-8-(2,3,4-trimethoxystyryl)xanthine (Compound 79)

Substantially the same procedure as in Reference Example 70 was repeated using 2.5 g (12.6 mmol) of 5,6-diamino-1,3-diethyluracil and 2.3 g (13.9 mmol) of 2,3,4-trimethoxycinnamic acid. Then, the resultant crude crystals were recrystallized from dioxane/water to give 2.85 g (yield 57%) of Compound 79 as white crystals.

Melting Point: 276.3-277.0 • C

Elemental Analysis: $C_{20}H_{24}N_4O_5$			
Calcd. (%):	C, 59.99;	H, 6.04;	N, 13.99
Found (%):	C, 60.26;	H, 6.24;	N, 14.28

IR (KBr) ν_{max} (cm^{-1}): 1696, 1655, 1500

NMR (270MHz; $CDCl_3$) δ (ppm): 12.39(1H, brs), 7.88(1H, d, J=16.3Hz), 7.30(1H, d, J=8.4Hz), 7.09-(1H, d, J=16.3Hz), 6.73(1H, d, J=8.4Hz), 4.26(2H, q, J=6.9Hz), 4.20(2H, q, J=6.9Hz), 3.96(3H, s), 3.92 (3H, s), 3.91(3H, s), 1.41(3H, t, J=6.9Hz), 1.29 (3H, t, J=6.9Hz)

Reference Example 77

(E)-1,3-Diethyl-7-methyl-8-(2,3,4-trimethoxystyryl)xanthine (Compound 80)

Substantially the same procedure as in Reference Example 1 was repeated using 1.5 g (3.75 mmol) of Compound 79 obtained in Reference Example 76 in place of Compound B. Then, the resultant crude crystals were recrystallized from hexane/ethyl acetate to give 1.32 g (yield 85%) of Compound 80 as colorless needles.

Melting Point: 152.9-154.3 °C

Elemental Analysis: $C_{21}H_{26}N_4O_5$			
Calcd. (%):	C, 60.86;	H, 6.32;	N, 13.52
Found (%):	C, 61.04;	H, 6.44;	N, 13.79

IR (KBr) ν_{max} (cm^{-1}): 1695, 1655, 1498, 1289

NMR (270MHz; $CDCl_3$) δ (ppm): 7.88(1H, d, J=15.8Hz), 7.28(1H, d, J=8.9Hz), 7.01(1H, d, J=15.8Hz), 6.72 (1H, d, J=8.9Hz), 4.22(2H, q, J=6.9Hz), 4.09(2H, q, J=6.9Hz), 4.04(3H, s), 3.97(3H, s), 3.91(3H, s), 3.90(3H, s), 1.38-(3H, t, J=6.9Hz), 1.27(3H, t, J=6.9Hz)

Reference Example 78

(E)-1,3-Diethyl-8-(4-methoxy-2,3-dimethylstyryl)xanthine (Compound 81)

Substantially the same procedure as in Reference Example 70 was repeated using 2.5 g (12.6 mmol) of 5,6-diamino-1,3-diethyluracil and 2.9 g (13.9 mmol) of 4-methoxy-2,3-dimethylcinnamic acid. Then, the resultant crude crystals were recrystallized from ethanol/water to give 0.80 g (yield 17%) of Compound 81 as white crystals.

Melting Point: >280.0 °C

Elemental Analysis: $C_{20}H_{24}N_4O_3$			
Calcd. (%):	C, 65.20;	H, 6.56;	N, 15.21
Found (%):	C, 65.24;	H, 6.61;	N, 15.29

IR (KBr) ν_{max} (cm^{-1}): 1697, 1642, 1496, 1270

NMR (270MHz; DMSO-d_6) δ (ppm): 13.52(1H, brs), 7.93 (1H, d, J=15.8Hz), 7.56(1H, d, J=8.2Hz), 6.89(1H, d, J=8.2Hz), 6.82(1H, d, J=15.8Hz), 4.06(2H, q, J=6.9Hz), 3.94(2H, q, J=6.9Hz), 3.81(3H, s), 2.33 (3H, s), 2.13-(3H, s), 1.26(3H, t, J=6.9Hz), 1.14 (3H, t, J=6.9Hz)

Reference Example 79

(E)-1,3-Diethyl-8-(4-methoxy-2,3-dimethylstyryl)-7-methylxanthine (Compound 82)

Substantially the same procedure as in Reference Example 1 was repeated using 500 mg (1.36 mmol) of Compound 81 obtained in Reference Example 78 in place of Compound B. Then, the resultant crude crystals were recrystallized from hexane/ethyl acetate to give 493 mg (yield 95%) of Compound 82 as pale yellow needles.

Melting Point: 207.7-208.3 °C

Elemental Analysis: $C_{21}H_{26}N_4O_3$			
Calcd. (%):	C, 65.95;	H, 6.85;	N, 14.65
Found (%):	C, 66.24;	H, 6.99;	N, 14.69

IR (KBr) ν_{max} (cm^{-1}): 1698, 1651, 1267

NMR (270MHz; $CDCl_3$) δ (ppm): 8.08(1H, d, J=15.2Hz), 7.46(1H, d, J=8.9Hz), 6.77(1H, d, J=8.9Hz), 6.67 (1H, d, J=15.2Hz), 4.22(2H, q, J=6.9Hz), 4.09(2H, q, J=6.9Hz), 4.03(3H, s), 3.86(3H, s), 2.40(3H, s), 2.21(3H, s), 1.39(3H, t, J=6.9Hz), 1.26(3H, t, J=6.9Hz)

Reference Example 80

(E)-1,3-Diethyl-8-(4-methoxy-2,5-dimethylstyryl)xanthine (Compound 83)

Substantially the same procedure as in Reference Example 70 was repeated using 2.5 g (12.6 mmol) of 5,6-diamino-1,3-diethyluracil and 2.9 g (13.9 mmol) of 4-methoxy-2,5-dimethylcinnamic acid. Then, the resultant crude crystals were recrystallized from dioxane/water to give 2.43 g (yield 52%) of Compound 83 as white crystals.

Melting Point: >280.0 °C

Elemental Analysis: $C_{20}H_{24}N_4O_3$			
Calcd. (%):	C, 65.20;	H, 6.56;	N, 15.21
Found (%):	C, 64.83;	H, 6.56;	N, 15.43

IR (KBr) ν_{max} (cm^{-1}): 1690, 1646, 1510, 1265

NMR (270MHz; DMSO-d_6) δ (ppm): 13.52(1H, brs), 7.82 (1H, d, J=16.3Hz), 7.54(1H, s), 6.86(1H, d, J=16.3Hz), 6.82(1H, s), 4.06(2H, q, J=6.9Hz), 3.94 (2H, q, J=6.9Hz), 3.81(3H, s), 2.41(3H, s), 2.14 (3H, s), 1.25(3H, t, J=6.9Hz), 1.14(3H, t, J=6.9Hz)

Reference Example 81

(E)-1,3-Diethyl-8-(4-methoxy-2,5-dimethylstyryl)-7-methylxanthine (Compound 84)

Substantially the same procedure as in Reference Example 1 was repeated using 1.10 g (2.98 mmol) of Compound 83 obtained in Reference Example 80 in place of Compound B. Then, the resultant crude crystals were recrystallized from ethyl acetate to give 0.76 g (yield 67%) of Compound 84 as yellow needles.

Melting Point: 235.4-236.1 °C

Elemental Analysis: $C_{21}H_{26}N_4O_3$			
Calcd. (%):	C, 65.95;	H, 6.85;	N, 14.65
Found (%):	C, 65.56;	H, 6.93;	N, 14.64

IR (KBr) ν_{max} (cm^{-1}): 1689, 1657, 1510, 1263

NMR (270MHz; $CDCl_3$) δ (ppm): 7.97(1H, d, J=15.5Hz), 7.42(1H, s), 6.71(1H, d, J=15.5Hz), 6.66(1H, s), 4.22(2H, q, J=6.9Hz), 4.09(2H, q, J=6.9Hz), 4.05 (3H, s), 3.86-(3H, s), 2.48(3H, s), 2.23(3H, s), 1.38(3H, t, J=6.9Hz), 1.26(3H, t, J=6.9Hz)

Reference Example 82

(E)-8-(2,4-Dimethoxy-3-methylstyryl)-1,3-diethylxanthine (Compound 85)

Substantially the same procedure as in Reference Example 70 was repeated using 2.0 g (10.1 mmol) of 5,6-diamino-1,3-diethyluracil and 2.04 g (9.19 mmol) of 2,4-dimethoxy-3-methylcinnamic acid. Then, the resultant crude crystals were recrystallized from dioxane/water to give 1.22 g (yield 32%) of Compound 85 as a yellow powder.

Melting Point: >275.0 °C

Elemental Analysis: $C_{20}H_{24}N_4O_4$			
Calcd. (%):	C, 62.48;	H, 6.29;	N, 14.57
Found (%):	C, 62.28;	H, 6.42;	N, 14.22

IR (KBr) ν_{max} (cm^{-1}): 1696, 1635, 1592, 1499

NMR (270MHz; DMSO-d_6) δ (ppm): 7.75(1H, d, J=16.5Hz), 7.58(1H, d, J=8.8Hz), 6.99(1H, d, J=16.5Hz), 6.85 (1H, d, J=8.8Hz), 4.04(2H, q, J=6.9Hz), 3.95-(2H, q, J=6.9Hz), 3.83(3H, s), 3.70(3H, s), 2.09(3H, s), 1.26(3H, t, J=6.9Hz), 1.14(3H, t, J=6.9Hz)

Reference Example 83

(E)-8-(2,4-Dimethoxy-3-methylstyryl)-1,3-diethyl-7-methylxanthine (Compound 86)

Substantially the same procedure as in Reference Example 1 was repeated using 700 mg (1.82 mmol) of Compound 85 obtained in Reference Example 82 in place of Compound B. Then, the resultant crude crystals were recrystallized from cyclohexane/toluene to give 610 mg (yield 84%) of Compound 86 as pale yellow needles.

Melting Point: 196.1-196.8 °C

Elemental Analysis: $C_{21}H_{26}N_4O_4$			
Calcd. (%):	C, 63.30;	H, 6.57;	N, 14.06
Found (%):	C, 63.32;	H, 6.74;	N, 14.13

IR (KBr) ν_{max} (cm^{-1}): 1695, 1649, 1498

NMR (270MHz; $CDCl_3$) δ (ppm): 7.81(1H, d, J=15.8Hz), 7.78(1H, d, J=8.6Hz), 7.23(1H, d, J=15.8Hz), 6.87 (1H, d, J=8.6Hz), 4.07(2H, q, J=6.9Hz), 4.01(3H, s), 3.92(2H, q, J=6.9Hz), 3.85(3H, s), 3.70(3H, s), 2.10(3H, s), 1.27-(3H, t, J=6.9Hz), 1.13(3H, t, J=6.9Hz)

Reference Example 84

(E)-1,3-Diethyl-8-(3,4-methylenedioxystyryl)xanthine (Compound 87)

Substantially the same procedure as in Reference Example 70 was repeated using 2.0 g (10.1 mmol) of 5,6-diamino-1,3-diethyluracil and 2.33 g (12.1 mmol) of 3,4-methylenedioxycinnamic acid. Then, the resultant crude crystals were recrystallized from dimethylformamide/water to give 1.34 g (yield 38%) of Compound 87 as a yellowish green powder.

Melting Point: >275.0 °C

Elemental Analysis: $C_{18}H_{18}N_4O_4$			
Calcd. (%):	C, 61.01;	H, 5.11;	N, 15.81
Found (%):	C, 61.16;	H, 5.03;	N, 15.80

IR (KBr) ν_{max} (cm^{-1}): 1685, 1638, 1499

NMR (270MHz; DMSO-d_6) δ (ppm): 7.55(1H, d, J=16.3Hz), 7.30(1H, s), 7.08(1H, d, J=8.9Hz), 6.96-(1H, d, J=8.9Hz), 6.90(1H, d, J=16.3Hz), 6.07(2H, s), 4.05 (2H, q, J=6.9Hz), 3.93(2H, q, J=6.9Hz), 1.25(3H, t, J=6.9Hz), 1.10-(3H, t, J=6.9Hz)

Reference Example 85

(E)-1,3-Diethyl-7-methyl-8-(3,4-methylenedioxystyryl)xanthine (Compound 88)

Substantially the same procedure as in Reference Example 1 was repeated using 1.35 g (3.81 mmol) of Compound 87 obtained in Reference Example 84 in place of Compound B. Then, the resultant crude crystals were recrystallized from cyclohexane/toluene to give 940 mg (yield 67%) of Compound 88 as yellow needles.

Melting Point: 219.4-219.6 °C

Elemental Analysis: $C_{19}H_{20}N_4O_4$			
Calcd. (%):	C, 61.94;	H, 5.47;	N, 15.20
Found (%):	C, 62.09;	H, 5.41;	N, 15.16

IR (KBr) ν_{max} (cm^{-1}): 1687, 1657, 1569, 1498, 1443

NMR (270MHz; $CDCl_3$) δ (ppm): 7.70(1H, d, J=15.5Hz), 7.10(1H, d, J=1.6Hz), 7.06(1H, dd, J=8.0, 1.6Hz), 6.84(1H, d, J=8.0Hz), 6.73(1H, d, J=15.5Hz), 6.02 (2H, s), 4.21(2H, q, J=6.9Hz), 4.09(2H, q, J=6.9Hz), 4.04(3H, s), 1.38(3H, t, J=6.9Hz), 1.26 (3H, t, J=6.9Hz)

Reference Example 86

(E)-8-[2-(1,4-Benzodioxan-6-yl)vinyl]-1,3-diethylxanthine (Compound 89)

Substantially the same procedure as in Reference Example 70 was repeated using 2.85 g (14.4 mmol) of 5,6-diamino-1,3-diethyluracil and 2.70 g (13.1 mmol) of 3-(1,4-benzodioxan-6-yl)acrylic acid. Then, the resultant crude crystals were recrystallized from dioxane/water to give 2.45 g (yield 51%) of Compound 89 as a pale yellow powder.

Melting Point: >300 °C

Elemental Analysis: $C_{19}H_{20}N_4O_4$			
Calcd. (%):	C, 61.94;	H, 5.47;	N, 15.20
Found (%):	C, 61.97;	H, 5.62;	N, 15.07

IR (KBr) ν_{max} (cm^{-1}): 1682, 1637, 1511, 1310

NMR (270MHz; DMSO-d_6) δ (ppm): 7.51(1H, d, J=16.2Hz), 7.10-7.03(2H, m), 6.89(1H, d, J=7.9Hz), 6.87(1H, d, J=16.2Hz), 4.27(4H, s), 4.05(2H, q, J=6.9Hz), 3.93-(2H, q, J=6.9Hz), 1.22(3H, t, J=6.9Hz), 1.13 (3H, t, J=6.9Hz)

Reference Example 87

(E)-8-[2-(1,4-Benzodioxan-6-yl)vinyl]-1,3-diethyl-7-methylxanthine (Compound 90)

Substantially the same procedure as in Reference Example 1 was repeated using 2.00 g (5.43 mmol) of Compound 89 obtained in Reference Example 86 in place of Compound B. Then, the resultant crude crystals were recrystallized from ethanol/2-propanol to give 1.58 g (yield 76%) of Compound 90 as yellow needles.

Melting Point: 233.1-233.6 °C

Elemental Analysis: $C_{20}H_{22}N_4O_4$			
Calcd. (%):	C, 62.81;	H, 5.79;	N, 14.65
Found (%):	C, 62.55;	H, 5.80;	N, 14.60

IR (KBr) ν_{max} (cm^{-1}): 1689, 1654, 1509

NMR (270MHz; $CDCl_3$) δ (ppm): 7.67(1H, d, J=15.8Hz), 7.15-7.05(2H, m), 6.88(1H, d, J=8.3Hz), 6.75(1H, d, J=15.8Hz), 4.30(4H, s), 4.21(2H, q, J=6.9Hz), 4.08(2H, q, J=6.9Hz), 4.03(3H, s), 1.39(3H, t, J=6.9Hz), 1.35(3H, t, J=6.9Hz)

Reference Example 88

(E)-8-(2,3,4-Trimethoxystyryl)theophylline (Compound 91)

Substantially the same procedure as in Reference Example 70 was repeated using 5.00 g (29.4 mmol) of 5,6-diamino-1,3-dimethyluracil and 7.71 g (32.4 mmol) of 2,3,4-trimethoxycinnamic acid. Then, the resultant crude crystals were recrystallized from 2-propanol/water to give 3.78 g (yield 35%) of Compound 91 as an ocher powder.

Melting Point: 264.8-266.1 °C

Elemental Analysis: $C_{18}H_{20}N_4O_5$			
Calcd. (%):	C, 58.05;	H, 5.41;	N, 15.04
Found (%):	C, 58.28;	H, 5.38;	N, 15.20

IR (KBr) ν_{max} (cm^{-1}): 1697, 1651, 1505, 1297

NMR (270MHz; $CDCl_3$) δ (ppm): 12.78(1H, s), 7.91(1H, d, J=16.8Hz), 7.28(1H, d, J=9.4Hz), 7.13(1H, d, J=16.8Hz), 6.73(1H, d, J=9.4Hz), 3.95(3H, s), 3.92 (3H, s), 3.90-(3H, s), 3.69(3H, s), 3.54(3H, s)

Reference Example 89

(E)-8-(2,3,4-Trimethoxystyryl)caffeine (Compound 92)

Substantially the same procedure as in Reference Example 1 was repeated using 2.00 g (5.38 mmol) of Compound 91 obtained in Reference Example 88 in place of Compound B. Then, the resultant crude crystals were recrystallized from cyclohexane/toluene to give 1.68 g (yield 81%) of Compound 92 as a pale y llow powder.

Melting Point: 186.7-187.9 °C

Elemental Analysis: $C_{19}H_{22}N_4O_5$			
Calcd. (%):	C, 59.06;	H, 5.74;	N, 14.50
Found (%):	C, 59.27;	H, 5.72;	N, 14.60

IR (KBr) ν_{max} (cm^{-1}): 1694, 1655, 1596, 1544, 1501, 1295

NMR (270MHz; $CDCl_3$) δ (ppm): 7.90(1H, d, J=16.3Hz), 7.28(1H, d, J=7.9Hz), 7.01(1H, d, J=16.3Hz), 6.72 (1H, d, J=7.9Hz), 4.04(3H, s), 3.97(3H, s), 3.91 (3H, s), 3.90(3H, s), 3.64(3H, s), 3.42(3H, s)

Reference Example 90

(E)-8-(4-Methoxy-2,3-dimethylstyryl)theophylline (Compound 93)

Substantially the same procedure as in Reference Example 70 was repeated using 1.74 g (10.2 mmol) of 5,6-diamino-1,3-dimethyluracil and 2.42 g (11.8 mmol) of 4-methoxy-2,3-dimethylcinnamic acid. Then, the resultant crude crystals were recrystallized from acetonitrile to give 750 mg (yield 22%) of Compound 93 as a white powder.

Melting Point: >275 °C

Elemental Analysis: $C_{18}H_{20}N_4O_3$			
Calcd. (%):	C, 63.51;	H, 5.92;	N, 16.46
Found (%):	C, 63.56;	H, 5.82;	N, 16.30

IR (KBr) ν_{max} (cm^{-1}): 1703, 1634, 1593

NMR (270MHz; DMSO-d_6) δ (ppm): 13.45(1H, s), 7.93(1H, d, J=16.2Hz), 7.53(1H, d, J=8.9Hz), 6.88-(1H, d, J=8.9Hz), 6.79(1H, d, J=16.2Hz), 3.80(3H, s), 3.75 (3H, s), 3.25(3H, s), 2.32(3H, s), 2.12(3H, s)

Reference Example 91

(E)-8-(4-Methoxy-2,3-dimethylstyryl)caffeine (Compound 94)

Substantially the same procedure as in Reference Example 1 was repeated using 500 mg (1.47 mmol) of Compound 93 obtained in Reference Example 90 in place of Compound B. Then, the resultant crude crystals were recrystallized from toluene to give 280 mg (yield 54%) of Compound 94 as a pale yellow powder.

Melting Point: >275 °C

Elemental Analysis: $C_{19}H_{22}N_4O_3$			
Calcd. (%):	C, 64.39;	H, 6.25;	N, 15.80
Found (%):	C, 64.44;	H, 6.27;	N, 16.11

IR (KBr) ν_{max} (cm^{-1}): 1694, 1650, 1544, 1491, 1435

NMR (270MHz; $CDCl_3$) δ (ppm): 7.96(1H, d, J=15.5Hz), 7.73(1H, d, J=8.6Hz), 7.07(1H, d, J=15.5Hz), 6.90 (1H, d, J=8.6Hz), 4.02(3H, s), 3.82(3H, s), 3.48 (3H, s), 3.29(3H, s), 2.32(3H, s), 2.13(3H, s)

Reference Example 92

(E)-8-(3,4-Methylenedioxystyryl)theophylline (Compound 95)

Substantially the same procedure as in Reference Example 70 was repeated using 5.0 g (29.4 mmol) of 5,6-diamino-1,3-dimethyluracil and 6.78 g (35.3 mmol) of 3,4-methylenedioxycinnamic acid. Then, the resultant crude crystals were recrystallized from dimethylformamide/water to give 1.20 g (yield 13%) of

Compound 95 as a pale yellow powder.

Melting Point: >275 °C

Elemental Analysis: $C_{16}H_{14}N_4O_4$			
Calcd. (%):	C, 58.99;	H, 4.32;	N, 17.16
Found (%):	C, 58.84;	H, 4.30;	N, 16.97

IR (KBr) ν_{max} (cm^{-1}): 1692, 1642, 1499

NMR (270MHz; DMSO-d_6) δ (ppm): 7.57(1H, d, J=16.1Hz), 7.09(1H, s), 7.07(1H, d, J=7.9Hz), 6.92-(1H, d, J=7.9Hz), 6.88(1H, d, J=16.1Hz), 6.07(2H, s), 3.47 (3H, s), 3.30(3H, s)

Reference Example 93

(E)-8-(3,4-Methylenedioxystyryl)caffeine (Compound 96)

Substantially the same procedure as in Reference Example 1 was repeated using 2.32 g (7.13 mmol) of Compound 95 obtained in Reference Example 92 in place of Compound B. Then, the resultant crude crystals were recrystallized from dioxane to give 1.54 g (yield 64%) of Compound 96 as yellow needles.

Melting Point: >300 °C

Elemental Analysis: $C_{17}H_{16}N_4O_4$			
Calcd. (%):	C, 59.99;	H, 4.73;	N, 16.46
Found (%):	C, 59.98;	H, 4.66;	N, 16.38

IR (KBr) ν_{max} (cm^{-1}): 1702, 1663, 1545, 1506

NMR (270MHz; $CDCl_3$) δ (ppm): 7.72(1H, d, J=15.3Hz), 7.10(1H, d, J=1.5Hz), 7.06(1H, dd, J=7.9, 1.5Hz), 6.84(1H, d, J=7.9Hz), 6.73(1H, d, J=15.3Hz), 6.03 (2H, s), 4.05(3H, s), 3.63(3H, s), 3.42(3H, s)

Reference Example 94

(E)-8-(2,3-Dimethoxystyryl)theophylline (Compound 97)

Substantially the same procedure as in Reference Example 70 was repeated using 2.50 g (14.7 mmol) of 5,6-diamino-1,3-dimethyluracil and 3.37 g (16.2 mmol) of 2,3-dimethoxycinnamic acid. Then, the resultant crude crystals were recrystallized from ethanol/water to give 1.03 g (yield 41%) of Compound 97 as pale yellow needles.

Melting Point: 289.2-290.5 °C

Elemental Analysis: $C_{17}H_{18}N_4O_4$			
Calcd. (%):	C, 59.64;	H, 5.29;	N, 16.36
Found (%):	C, 59.42;	H, 5.12;	N, 16.65

IR (KBr) ν_{max} (cm^{-1}): 1700, 1649, 1499, 1476, 1273

NMR (270MHz; DMSO-d_6) δ (ppm): 13.60(1H, brs), 7.84 (1H, d, J=16.8Hz), 7.26(1H, d, J=6.9Hz), 7.15-7.00 (3H, m), 3.83(3H, s), 3.79(3H, s), 3.48(3H, s), 3.26(3H, s)

Reference Example 95

(E)-8-(2,3-Dimethoxystyryl)caffeine (Compound 98)

Substantially the same procedure as in Reference Example 1 was repeated using 1.10 g (3.22 mmol) of Compound 97 obtained in Reference Example 94 in place of Compound B. Then, the resultant crude crystals were recrystallized from toluene to give 570 mg (yield 50%) of Compound 98 as yellow needles.

Melting Point: 233.6-236.7 °C

Elemental Analysis: $C_{18}H_{20}N_4O_4$			
Calcd. (%):	C, 60.66;	H, 5.65;	N, 15.72
Found (%):	C, 60.21;	H, 5.74;	N, 16.13

IR (KBr) ν_{max} (cm^{-1}): 1688, 1645, 1545, 1480

NMR (270MHz; DMSO-d_6) δ (ppm): 7.91(1H, d, J = 16.0Hz), 7.52(1H, dd, J = 7.6, 1.7Hz), 7.32(1H, d, J = 16.0Hz), 7.10-7.05(2H, m), 4.03(3H, s), 3.84(3H, s), 3.79 (3H, s), 3.48(3H, s), 3.24(3H, s)

Reference Example 96

(E)-8-(2,4-Dimethoxystyryl)theophylline (Compound 99)

Substantially the same procedure as in Reference Example 70 was repeated using 1.0 g (5.88 mmol) of 5,6-diamino-1,3-dimethyluracil and 1.35 g (6.48 mmol) of 2,4-dimethoxycinnamic acid. Then, the resultant crude crystals were recrystallized from dimethylformamide to give 221 mg (yield 11%) of Compound 99 as pale yellow grains.

Melting Point: >280 °C

Elemental Analysis: $C_{17}H_{18}N_4O_4$			
Calcd. (%):	C, 59.64;	H, 5.29;	N, 16.36
Found (%):	C, 59.51;	H, 5.34;	N, 16.58

IR (KBr) ν_{max} (cm^{-1}): 1705, 1650, 1607, 1505

NMR (270MHz; DMSO-d_6) δ (ppm): 13.40(1H, brs), 7.78 (1H, d, J = 16.5Hz), 7.53(1H, d, J = 8.3Hz), 6.93(1H, d, J = 16.5Hz), 6.63(1H, d, J = 2.3Hz), 6.60(1H, dd, J = 8.3, 2.3Hz), 3.89(3H, s), 3.82(3H, s), 3.47(3H, s), 3.25(3H, s)

Reference Example 97

(E)-8-(2,4-Dimethoxystyryl)caffeine (Compound 100)

Substantially the same procedure as in Reference Example 1 was repeated using 700 mg (2.05 mmol) of Compound 99 obtained in Reference Example 96 in place of Compound B. Then, the resultant crude crystals were recrystallized from dioxane to give 621 mg (yield 85%) of Compound 100 as yellow needles.

Melting Point: 241.5-242.1 °C

Elemental Analysis: $C_{18}H_{20}N_4O_4$			
Calcd. (%):	C, 60.66;	H, 5.65;	N, 15.72
Found (%):	C, 60.49;	H, 5.61;	N, 15.69

IR (KBr) ν_{max} (cm^{-1}): 1685, 1650, 1602, 1434

NMR (270MHz; $CDCl_3$) δ (ppm): 7.95(1H, d, J = 15.8Hz), 7.48(1H, d, J = 8.6Hz), 6.98(1H, d, J = 15.8Hz), 6.54 (1H, dd, J = 8.6, 2.3Hz), 6.49(1H, d, J = 2.3Hz), 4.03 (3H, s), 3.92(3H, s), 3.86(3H, s), 3.64(3H, s), 3.42(3H, s)

Reference Example 98

(E)-8-(4-Methoxy-2,5-dimethylstyryl)theophylline (Compound 101)

Substantially the same procedure as in Reference Example 70 was repeated using 1.0 g (5.88 mmol) of 5,6-diamino-1,3-dimethyluracil and 1.33 g (6.45 mmol) of 4-methoxy-2,5-dimethylcinnamic acid. Then, the resultant crude crystals were recrystallized from dimethylformamide to give 393 mg (yield 20%) of Compound 101 as pale yellow grains.

Melting Point: >280 °C

Elemental Analysis: $C_{18}H_{20}N_4O_3$			
Calcd. (%):	C, 63.51;	H, 5.92;	N, 16.46
Found (%):	C, 63.59;	H, 6.10;	N, 16.23

IR (KBr) ν_{max} (cm^{-1}): 1703, 1648, 1509, 1260

NMR (270MHz; DMSO-d_6) δ (ppm): 13.48(1H, brs), 7.81 (1H, d, J=16.2Hz), 7.50(1H, s), 6.82(1H, d, J=16.2Hz), 6.81(1H, s), 3.81(3H, s), 3.46(3H, s), 3.25(3H, s), 2.40(3H, s), 2.14(3H, s)

Reference Example 99

(E)-8-(4-Methoxy-2,5-dimethylstyryl)caffeine (Compound 102)

Substantially the same procedure as in Reference Example 1 was repeated using 300 mg (0.88 mmol) of Compound 101 obtained in Reference Example 98 in place of Compound B. Then, the resultant crude crystals were recrystallized from dioxane to give 211 mg (yield 68%) of Compound 102 as yellow needles.

Melting Point: >280 °C

MS-EI m/e: 354(M^+), 339(M^+-CH_3)

IR (KBr) ν_{max} (cm^{-1}): 1692, 1653, 1508

NMR (270MHz; $CDCl_3$) δ (ppm): 8.00(1H, d, J=15.3Hz), 7.42(1H, s), 6.72(1H, d, J=15.3Hz), 6.66(1H, s), 4.06(3H, s), 3.86(3H, s), 3.64(3H, s), 3.42(3H, s), 2.49(3H, s), 2.23-(3H, s)

Reference Example 100

(E)-8-(2,4-Dimethoxy-3-methylstyryl)theophylline (Compound 103)

Substantially the same procedure as in Reference Example 70 was repeated using 1.0 g (5.88 mmol) of 5,6-diamino-1,3-dimethyluracil and 1.44 g (6.45 mmol) of 2,4-dimethoxy-3-methylcinnamic acid. Then, the resultant crude crystals were recrystallized from dioxane to give 581 mg (yield 28%) of Compound 103 as pale yellow needles.

Melting Point: >280 °C

Elemental Analysis: $C_{18}H_{20}N_4O_4$			
Calcd. (%):	C, 60.67;	H, 5.65;	N, 15.72
Found (%):	C, 60.34;	H, 5.77;	N, 15.64

IR (KBr) ν_{max} (cm^{-1}): 1695, 1653, 1499, 1270

NMR (270MHz; DMSO-d_6) δ (ppm): 13.52(1H, brs), 7.75 (1H, d, J=16.2Hz), 7.55(1H, d, J=8.3Hz), 6.96(1H, d, J=16.2Hz), 6.84(1H, d, J=8.3Hz), 3.83(3H, s), 3.70-(3H, s), 3.47(3H, s), 3.25(3H, s), 2.09(3H, s)

Reference Example 101

(E)-8-(2,4-Dimethoxy-3-methylstyryl)caffeine (Compound 104)

Substantially the same procedure as in Reference Example 1 was repeated using 300 mg (0.84 mmol) of Compound 103 obtained in Reference Example 100 in place of Compound B. Then, the resultant crude crystals were recrystallized from methylene chloride/ether to give 239 mg (yield 77%) of Compound 104 as white needles.

Melting Point: 252.7-253.5 °C

Elemental Analysis: $C_{19}H_{22}N_4O_4$			
Calcd. (%):	C, 61.61;	H, 5.98;	N, 15.13
Found (%):	C, 61.40;	H, 6.06;	N, 15.17

IR (KBr) ν_{max} (cm^{-1}): 1692, 1651, 1505

NMR (270MHz; $CDCl_3$) δ (ppm): 7.92(1H, d, J=15.8Hz), 7.42(1H, d, J=8.9Hz), 6.99(1H, d, J=15.8Hz), 6.70 (1H, d, J=8.9Hz), 4.04(3H, s), 3.88(3H, s), 3.78 (3H, s), 3.64(3H, s), 3.42(3H, s), 2.19(3H, s)

Reference Example 102

(E)-8-(2-Chloro-3,4-dimethoxystyryl)-1,3-diethylxanthine (Compound 105)

Substantially the same procedure as in Reference Example 70 was repeated using 2.00 g (10.1 mmol) of 5,6-diamino-1,3-diethyluracil and 2.94 g (12.1 mmol) of 2-chloro-3,4-dimethoxycinnamic acid. Then, the resultant crude crystals were recrystallized from 2-propanol/water to give 2.19 g (yield 54%) of Compound 105 as pale yellow needles.

Melting Point: 278.0-280.9 °C

Elemental Analysis: $C_{19}H_{21}ClN_4O_4$			
Calcd. (%):	C, 56.36;	H, 5.22;	N, 13.83
Found (%):	C, 56.13;	H, 5.21;	N, 13.67

IR (KBr) ν_{max} (cm^{-1}): 1705, 1642, 1499

NMR (270MHz; DMSO-d_6) δ (ppm): 7.88(1H, d, J=16.3Hz), 7.64(1H, d, J=8.9Hz), 7.13(1H, d, J=8.9Hz), 7.00 (1H, d, J=16.3Hz), 4.06(2H, q, J=7.1Hz), 3.98-3.88 (2H, m), 3.88(3H, s), 3.77(3H, s), 1.26(3H, t, J=7.1Hz), 1.14-(3H, t, J=6.9Hz)

Reference Example 103

(E)-8-(2-Chloro-3,4-dimethoxystyryl)-1,3-diethyl-7-methylxanthine (Compound 106)

Substantially the same procedure as in Reference Example 1 was repeated using 1.80 g (4.45 mmol) of Compound 105 obtained in Reference Example 102 in place of Compound B. Then, the resultant crude crystals were recrystallized from 2-propanol/water to give 1.20 g (yield 64%) of Compound 106 as yellow needles.

Melting Point: 204.6-205.4 °C

Elemental Analysis: $C_{20}H_{23}ClN_4O_4$			
Calcd. (%):	C, 57.34;	H, 5.53;	N, 13.37
Found (%):	C, 57.46;	H, 5.67;	N, 13.10

IR (KBr) ν_{max} (cm^{-1}): 1696, 1657, 1496, 1439, 1292

NMR (270MHz; DMSO-d_5) δ (ppm): 7.92(1H, d, J=15.8Hz), 7.86(1H, d, J=8.9Hz), 7.29(1H, d, J=15.8Hz), 7.16 (1H, d, J=8.9Hz), 4.11-4.03(2H, m), 4.03(3H, s), 3.96-3.90(2H, m), 3.90(3H, s), 3.77(3H, s), 1.26 (3H, t, J=6.9Hz), 1.13(3H, t, J=6.9Hz)

Reference Example 104

(E)-8-(2-Chloro-3,4-dimethoxystyryl)theophylline (Compound 107)

2-Chloro-3,4-dimethoxycinnamic acid (3.93 g, 16.2 mmol) was dissolved in 57 ml of pyridine. To the solution was added 1.26 ml (17.6 mmol) of thionyl chloride under ice cooling, and the mixture was stirred at 60°C for 1.5 hours. Methylene chloride (58 ml) containing 2.50g (14.7 mmol) of 5,6-diamino-1,3-dimethyluracil was added dropwise to the solution under ice cooling, and the reaction solution was stirred at room temperature for further 40 minutes. The deposited crystals were collected by filtration and the obtained crude crystals were dissolved in a mixture of 68 ml of an aqueous 2N sodium hydroxide solution, 68 ml of dioxane, and 34 ml of water, followed by heating under reflux for 30 minutes. After cooling, the solution was neutralized with a concentrated aqueous solution of hydrochloric acid, and the deposited crystals were collected by filtration. The collected crystals were washed with water, dried, and recrystallized from dimethylformamide/ water to give 1.55 g (yield 30%) of Compound 107 as pale yellow needles.

Melting Point: 241.6-242.6 • C

Elemental Analysis: $C_{17}H_{17}ClN_4O_4$			
Calcd. (%):	C, 54.18;	H, 4.54;	N, 14.86
Found (%):	C, 54.31;	H, 4.54;	N, 14.43

IR (KBr) ν_{max} (cm^{-1}): 1704, 1653, 1496, 1300

NMR (270MHz; DMSO-d_6) δ (ppm): 7.88(1H, d, J=16.2Hz), 7.62(1H, d, J=8.9Hz), 7.13(1H, d, J=8.9Hz), 6.97 (1H, d, J=16.2Hz), 3.88(3H, s), 3.77(3H, s), 3.47 (3H, s), 3.25(3H, s)

Reference Example 105

(E)-8-(2-Chloro-3,4-dimethoxystyryl)caffeine (Compound 108)

Substantially the same procedure as in Reference Example 1 was repeated using 1.0 g (2.66 mmol) of Compound 107 obtained in Reference Example 104 in place of Compound B. Then, the resultant crude crystals were recrystallized from toluene to give 840 mg (yield 81%) of Compound 108 as a yellow powder.

Melting Point: 284.6-288.0 • C

Elemental Analysis: $C_{18}H_{19}ClN_4O_4$			
Calcd. (%):	C, 55.31;	H, 4.59;	N, 14.33
Found (%):	C, 55.40;	H, 4.83;	N, 14.09

IR (KBr) ν_{max} (cm^{-1}): 1688, 1650, 1493, 1290

NMR (270MHz; $CDCl_3$) δ (ppm): 8.10(1H, d, J=15.8Hz), 7.43(1H, d, J=8.8Hz), 6.88(1H, d, J=8.8Hz), 6.83 (1H, d, J=15.8Hz), 4.06(3H, s), 3.93(3H, s), 3.90 (3H, s), 3.64-(3H, s), 3.42(3H, s)

Reference Example 106

(E)-8-(2,5-Dimethylstyryl)-1,3-diethylxanthine (Compound 109)

Substantially the same procedure as in Reference Example 70 was repeated using 3.00 g (15.1 mmol) of 5,6-diamino-1,3-diethyluracil and 3.20 g (18.2 mmol) of 2,5-dimethylcinnamic acid. Then, the resultant crude crystals were recrystallized from ethanol/toluene to give 2.56 g (yield 50%) of Compound 109 as white needles.

Melting Point: 281.8-282.5 • C

Elemental Analysis: $C_{19}H_{22}N_4O_2 \cdot 0.5H_2O$			
Calcd. (%):	C, 66.46;	H, 6.97;	N, 15.50
Found (%):	C, 66.77;	H, 6.82;	N, 15.72

IR (KBr) ν_{max} (cm^{-1}): 1706, 1639, 1503

NMR (270MHz; DMSO-d_6) δ (ppm): 7.84(1H, d, J = 16.3Hz), 7.53(1H, s), 7.13(1H, d, J = 7.4Hz), 7.06-(1H, d, J = 7.4Hz), 7.00(1H, d, J = 16.3Hz), 4.06(2H, q, J = 7.1Hz), 3.94(2H, q, J = 7.1Hz), 2.37(3H, s), 2.30 (3H, s), 1.26(3H, t, J = 7.1Hz), 1.14(3H, t, J = 7.1Hz)

Reference Example 107

(E)-8-(2,5-Dimethylstyryl)-1,3-diethyl-7-methylxanthine(Compound 110)

Substantially the same procedure as in Reference Example 1 was repeated using 2.00 g (5.92 mmol) of Compound 109 obtained in Reference Example 106 in place of Compound B. Then, the resultant crude crystals were recrystallized from toluene/cyclohexane to give 1.29 g (yield 62%) of Compound 110 as white needles.

Melting Point: 190.3-190.7 • C

Elemental Analysis: $C_{20}H_{24}N_4O_2$			
Calcd. (%):	C, 68.16;	H, 6.86;	N, 15.89
Found (%):	C, 68.15;	H, 7.02;	N, 15.65

IR (KBr) ν_{max} (cm^{-1}): 1698, 1657

NMR (270MHz; $CDCl_3$) δ (ppm): 7.86(1H, d, J = 15.8Hz), 7.71(1H, s), 7.23(1H, d, J = 15.8Hz), 7.15(1H, d, J = 7.9Hz), 7.09(1H, d, J = 7.9Hz), 4.11-4.04(2H, m), 4.04(3H, s), 3.92(2H, q, J = 6.9Hz), 2.37(3H, s), 2.32(3H, s), 1.26(3H, t, J = 6.9Hz), 1.13(3H, t, J = 6.9Hz)

Reference Example 108

(E)-8-(3,4-Difluorostyryl)-1,3-diethylxanthine (Compound 111)

Substantially the same procedure as in Reference Example 70 was repeated using 2.50 g (12.6 mmol) of 5,6-diamino-1,3-diethyluracil and 2.79 g (15.2 mmol) of 3,4-difluorocinnamic acid. Then, the resultant crude crystals were recrystallized from dioxane/water to give 2.12 g (yield 49%) of Compound 111 as gray plates.

Melting Point: >300 • C

Elemental Analysis: $C_{17}H_{16}F_2N_4O_2$			
Calcd. (%):	C, 58.95;	H, 4.65;	N, 16.17
Found (%):	C, 59.25;	H, 4.59;	N, 16.42

IR (KBr) ν_{max} (cm^{-1}): 1688, 1640, 1519

NMR (270MHz; DMSO-d_6) δ (ppm): 7.78(1H, dd, J=11.4, 7.1Hz), 7.60(1H, d, J=16.3Hz), 7.50-7.45-(2H, m), 7.07(1H, d, J=16.3Hz), 4.06(2H, q, J=7.0Hz), 3.94 (2H, q, J=7.1Hz), 1.26(3H, t, J=7.0Hz), 1.14(3H, t, J=7.1Hz)

Reference Example 109

(E)-8-(3,4-Difluorostyryl)-1,3-diethyl-7-methylxanthine(Compound 112)

Substantially the same procedure as in Reference Example 1 was repeated using 1.70 g (4.91 mmol) of Compound 111 obtained in Reference Example 108 in place of Compound B. Then, the resultant crude crystals were recrystallized from toluene/cyclohexane to give 1.29 g (yield 73%) of Compound 112 as yellow needles.

Melting Point: 208.5-210.8 °C

Elemental Analysis: $C_{18}H_{18}F_2N_4O_2$			
Calcd. (%):	C, 59.99;	H, 5.03;	N, 15.54
Found (%):	C, 60.09;	H, 5.04;	N, 15.19

IR (KBr) ν_{max} (cm^{-1}): 1688, 1652, 1545, 1520, 1441

NMR (270MHz; DMSO-d_6) δ (ppm): 8.02(1H, ddd, J=12.4, 7.7, 2.0Hz), 7.65-7.60(1H, m), 7.61(1H, d, J=15.8Hz), 7.54-7.43(1H, m), 7.40(1H, d, J=15.8Hz), 4.08-4.04-(2H, m), 4.04(3H, s), 3.92(2H, q, J=6.9Hz), 1.26(3H, t, J=6.9Hz), 1.13(3H, t, J=6.9Hz)

Reference Example 110

(E)-8-(3-Bromo-4-methoxystyryl)-1,3-diethylxanthine (Compound 113)

Substantially the same procedure as in Reference Example 70 was repeated using 2.00 g (10.1 mmol) of 5,6-diamino-1,3-diethyluracil and 2.72 g (10.6 mmol) of 3-bromo-4-methoxycinnamic acid. Then, the resultant crude crystals were recrystallized from dioxane to give 726 mg (yield 17%) of Compound 113 as pale brown needles.

Melting Point: >280 °C

Elemental Analysis: $C_{18}H_{19}BrN_4O_3$			
Calcd. (%):	C, 51.57;	H, 4.57;	N, 13.36
Found (%):	C, 51.33;	H, 4.56;	N, 13.17

IR (KBr) ν_{max} (cm^{-1}): 1694, 1648, 1506, 1281, 1260

NMR (270MHz; DMSO-d_6) δ (ppm): 13.52(1H, brs), 7.87 (1H, d, J=2.0Hz), 7.63(1H, dd, J=8.4, 2.0Hz), 7.56 (1H, d, J=16.3Hz), 7.16(1H, d, J=8.4Hz), 6.95(1H, d, J=16.3Hz), 4.06(2H, q, J=6.9Hz), 3.93(2H, q, J=6.9Hz), 3.89-(3H, s), 1.26(3H, t, J=6.9Hz), 1.14 (3H, t, J=6.9Hz)

Reference Example 111

(E)-8-(3-Bromo-4-methoxystyryl)-1,3-diethyl-7-methylxanthine (Compound 114)

Substantially the same procedure as in Reference Example 1 was repeated using 400 mg (0.95 mmol) of Compound 113 obtained in Reference Example 110 in place of Compound B. Then, the resultant crude crystals were recrystallized from dioxane/water to give 332 mg (yield 80%) of Compound 114 as pale yellow needles.

Melting Point: 219.1-223.7 °C

Elemental Analysis: $C_{19}H_{21}BrN_4O_3$			
Calcd. (%):	C, 52.67;	H, 4.88;	N, 12.93
Found (%):	C, 52.79;	H, 4.97;	N, 12.70

IR (KBr) ν_{max} (cm^{-1}): 1686, 1651, 1541, 1501, 1435

NMR (270MHz; $CDCl_3$) δ (ppm): 7.83(1H, d, J=2.0Hz), 7.69(1H, d, J=15.8Hz), 7.48(1H, dd, J=8.4, 2.0Hz), 6.92(1H, d, J=8.4Hz), 6.78(1H, d, J=15.8Hz), 4.21 (2H, q, J=6.9Hz), 4.09(2H, q, J=6.9Hz), 4.06(3H, s), 3.95(3H, s), 1.38(3H, t, J=6.9Hz), 1.26(3H, t, J=6.9Hz)

Reference Example 112

(E)-8-(3-Bromo-4-methoxystyryl)theophylline (Compound 115)

Substantially the same procedure as in Reference Example 70 was repeated using 2.00 g (11.8 mmol) of 5,6-diamino-1,3-dimethyluracil and 3.32 g (12.9 mmol) of 3-bromo-4-methoxycinnamic acid. Then, the resultant crude crystals were recrystallized from dimethylformamide to give 2.00 g (yield 43%) of Compound 115 as a pale yellow powder.

Melting Point: >280 °C

Elemental Analysis: $C_{16}H_{15}BrN_4O_3$			
Calcd. (%):	C, 49.12;	H, 3.86;	N, 14.32
Found (%):	C, 49.16;	H, 3.80;	N, 14.06

IR (KBr) ν_{max} (cm^{-1}): 1691, 1644, 1598, 1499, 1257

NMR (270MHz; DMSO-d_6) δ (ppm): 13.41(1H, brs), 7.84 (1H, d, J=2.0Hz), 7.61(1H, dd, J=8.4, 2.0Hz), 7.56 (1H, d, J=16.3Hz), 7.15(1H, d, J=8.4Hz), 6.92(1H, d, J=16.3Hz), 3.89(3H, s), 3.47(3H, s), 3.26(3H, s)

Reference Example 113

(E)-8-(3-Bromo-4-methoxystyryl)caffeine (Compound 116)

Substantially the same procedure as in Reference Example 1 was repeated using 1.00 g (2.56 mmol) of Compound 115 obtained in Reference Example 112 in place of Compound B. Then, the resultant crude crystals were recrystallized from dioxane to give 877 mg (yield 85%) of Compound 116 as a yellow powder.

Melting Point: 283.3-283.4 °C

Elemental Analysis: $C_{17}H_{17}BrN_4O_3$			
Calcd. (%):	C, 50.39;	H, 4.23;	N, 13.83
Found (%):	C, 50.04;	H, 4.00;	N, 13.49

IR (KBr) ν_{max} (cm^{-1}): 1693, 1654, 1500

NMR (270MHz; $CDCl_3$) δ (ppm): 7.82(1H, d, J=2.0Hz), 7.70(1H, d, J=15.8Hz), 7.47(1H, dd, J=8.4, 2.0Hz), 6.92(1H, d, J=8.4Hz), 6.78(1H, d, J=15.8Hz), 4.07 (3H, s), 3.95(3H, s), 3.62(3H, s), 3.42(3H, s)

Reference Example 114

(E)-8-(2-Bromo-4,5-dimethoxystyryl)-1,3-diethylxanthine(Compound 117)

Substantially the same procedure as in Reference Example 70 was repeated using 3.00 g (15.1 mmol) of 5,6-diamino-1,3-diethyluracil and 4.78 g (17.2 mmol) of 2-bromo-4,5-dimethoxycinnamic acid. Then, the resultant crude crystals were recrystallized from dioxane to give 3.34 g (yield 49%) of Compound 117 as pale yellow needles.

Melting Point: >285 °C

Elemental Analysis: $C_{19}H_{21}BrN_4O_4$			
Calcd. (%):	C, 50.79;	H, 4.71;	N, 12.47
Found (%):	C, 50.49;	H, 4.64;	N, 12.36

IR (KBr) ν_{max} (cm^{-1}): 1693, 1621, 1509, 1260

NMR (270MHz; DMSO-d_6) δ (ppm): 13.65(1H, brs), 7.81 (1H, d, J=16.3Hz), 7.37(1H, s), 7.20(1H, s), 7.06 (1H, d, J=16.3Hz), 4.07(2H, q, J=6.9Hz), 3.95(2H, q, J=6.9Hz), 3.86(3H, s), 3.82(3H, s), 1.27(3H, t, J=6.9Hz), 1.15(3H, t, J=6.9Hz)

Reference Example 115

(E)-8-(2-Bromo-4,5-dimethoxystyryl)-1,3-diethyl-7-methylxanthine (Compound 118)

Substantially the same procedure as in Reference Example 1 was repeated using 1.50 g (3.34 mmol) of Compound 117 obtained in Reference Example 114 in place of Compound B. Then, the resultant crude crystals were recrystallized from hexane/ethyl acetate to give 1.43 g (yield 92%) of Compound 118 as yellow needles.

Melting Point: 234.2-234.9 °C

Elemental Analysis: $C_{20}H_{23}BrN_4O_4$			
Calcd. (%):	C, 51.85;	H, 5.00;	N, 12.09
Found (%):	C, 51.96;	H, 4.95;	N, 11.90

IR (KBr) ν_{max} (cm^{-1}): 1688, 1648, 1504, 1307, 1261

NMR (270MHz; $CDCl_3$) δ (ppm): 8.01(1H, d, J=15.8Hz), 7.11(1H, s), 7.09(1H, s), 6.76(1H, d, J=15.8Hz), 4.22(2H, q, J=6.9Hz), 4.09(2H, q, J=6.9Hz), 4.08 (3H, s), 3.95(3H, s), 3.92(3H, s), 1.39(3H, t, J=6.9Hz), 1.27(3H, t, J=6.9Hz)

Reference Example 116

(E)-8-(4,5-Dimethoxy-2-nitrostyryl)-1,3-diethylxanthine(Compound 119)

Substantially the same procedure as in Reference Example 70 was repeated using 1.50 g (7.57 mmol) of 5,6-diamino-1,3-diethyluracil and 2.11 g (8.33 mmol) of 4,5-dimethoxy-2-nitrocinnamic acid. Then, the resultant crude crystals were recrystallized from dioxane to give 1.22 g (yield 39%) of Compound 119 as orange needles.

Melting Point: 283.6-284.2 • C

Elemental Analysis: $C_{19}H_{21}N_5O_6$			
Calcd. (%):	C, 54.94;	H, 5.09;	N, 16.86
Found (%):	C, 54.90;	H, 5.07;	N, 16.88

IR (KBr) ν_{max} (cm^{-1}): 1692, 1641, 1520

NMR (270MHz; DMSO-d_6) δ (ppm): 7.99(1H, d, J=16.3Hz), 7.61(1H, s), 7.38(1H, s), 7.15(1H, d, J=16.3Hz), 4.06(2H, q, J=6.9Hz), 3.98(3H, s), 3.95(2H, q, J=6.9Hz), 3.89(3H, s), 1.26(3H, t, J=6.9Hz), 1.15 (3H, t, J=6.9Hz)

Reference Example 117

(E)-8-(4,5-Dimethoxy-2-nitrostyryl)-1,3-diethyl-7-methylxanthine (Compound 120)

Substantially the same procedure as in Reference Example 1 was repeated using 822 mg (1.98 mmol) of Compound 119 obtained in Reference Example 116 in place of Compound B. Then, the resultant crude crystals were recrystallized from ethyl acetate to give 762 mg (yield 90%) of Compound 120 as orange needles.

Melting Point: 246.3-246.8 • C

Elemental Analysis: $C_{20}H_{23}N_5O_6$			
Calcd. (%):	C, 55.94;	H, 5.40;	N, 16.31
Found (%):	C, 55.98;	H, 5.42;	N, 16.43

IR (KBr) ν_{max} (cm^{-1}): 1692, 1657, 1519, 1273

NMR (270MHz; $CDCl_3$) δ (ppm): 8.27(1H, d, J=15.8Hz), 7.66(1H, s), 7.03(1H, s), 6.77(1H, d, J=15.8Hz), 4.21(2H, q, J=6.9Hz), 4.10(3H, s), 4.09(2H, q, J=6.9Hz), 4.05(3H, s), 4.00(3H, s), 1.37(3H, t, J=6.9Hz), 1.27(3H, t, J=6.9Hz)

Reference Example 118

(E)-1,3-Diethyl-8-(3-methoxy-2-nitrostyryl)xanthine (Compound 121)

Substantially the same procedure as in Reference Example 70 was repeated using 2.50 g (12.6 mmol) of 5,6-diamino-1,3-diethyluracil and 3.10 g (13.9 mmol) of 3-methoxy-2-nitrocinnamic acid. Then, the resultant crude crystals were recrystallized from dioxane/water to give 2.28 g (yield 47%) of Compound 121 as orange needles.

Melting Point: >285 • C

Elemental Analysis: $C_{18}H_{19}N_5O_5$			
Calcd. (%):	C, 56.10;	H, 4.97;	N, 18.17
Found (%):	C, 56.37;	H, 4.88;	N, 17.85

IR (KBr) ν_{max} (cm^{-1}): 1695, 1640, 1533

NMR (270MHz; DMSO-d_6) δ (ppm): 13.88(1H, brs), 7.60-7.56(2H, m), 7.39(1H, d, J=16.3Hz), 7.32(1H, dd, J=6.9, 3.0Hz), 7.21(1H, d, J=16.3Hz), 4.05(2H, q, J=6.9Hz), 3.94(2H, q, J=6.9Hz), 3.91(3H, s), 1.25 (3H, t, J=6.9Hz), 1.14-(3H, t, J=6.9Hz)

Reference Example 119

(E)-1,3-Diethyl-8-(3-methoxy-2-nitrostyryl)-7-methylxanthine (Compound 122)

Substantially the same procedure as in Reference Example 1 was repeated using 688 mg (1.79 mmol) of Compound 121 obtained in Reference Example 118 in place of Compound B. Then, the resultant crude crystals were recrystallized from ethyl acetate to give 623 mg (yield 87%) of Compound 122 as yellow needles.

Melting Point: 258.4-259.9 • C

Elemental Analysis: $C_{19}H_{21}N_5O_5$			
Calcd. (%):	C, 57.14;	H, 5.30;	N, 17.53
Found (%):	C, 57.26;	H, 5.34;	N, 17.26

IR (KBr) ν_{max} (cm^{-1}): 1697, 1546, 1530

NMR (270MHz; $CDCl_3$) δ (ppm): 7.62(1H, d, J=15.3Hz), 7.46(1H, dd, J=8.4, 7.9Hz), 7.30(1H, d, J=7.9Hz), 7.05(1H, d, J=8.4Hz), 6.95(1H, d, J=15.3Hz), 4.19 (2H, q, J=6.9Hz), 4.08(2H, q, J=6.9Hz), 4.05(3H, s), 3.94(3H, s), 1.36(3H, t, J=6.9Hz), 1.26(3H, t, J=6.9Hz)

Reference Example 120

(E)-8-(4-Ethoxystyryl)-1,3-diethylxanthine (Compound 123)

Substantially the same procedure as in Reference Example 70 was repeated using 3.00 g (15.1 mmol) of 5,6-diamino-1,3-diethyluracil and 3.20 g (16.7 mmol) of 4-ethoxycinnamic acid. Then, the resultant crude crystals were recrystallized from dioxane to give 2.97 g (yield 55%) of Compound 123 as pale yellow needles.

Melting Point: 296.7-298.6 • C

Elemental Analysis: $C_{19}H_{22}N_4O_3$			
Calcd. (%):	C, 64.39;	H, 6.25;	N, 15.81
Found (%):	C, 64.54;	H, 6.52;	N, 15.80

IR (KBr) ν_{max} (cm^{-1}): 1695, 1647, 1516, 1250

NMR (270MHz; DMSO-d_6) δ (ppm): 13.36(1H, brs), 7.59 (1H, d, J=16.2Hz), 7.55(2H, d, J=8.6Hz), 6.96(2H, d, J=8.6Hz), 6.88(1H, d, J=16.2Hz), 4.11-4.04(4H, m), 3.94(2H, q, J=6.9Hz), 1.34(3H, t, J=6.9Hz), 1.26(3H, t, J=6.9Hz), 1.14(3H, t, J=6.9Hz)

Reference Example 121

(E)-8-(4-Ethoxystyryl)-1,3-diethyl-7-methylxanthine (Compound 124)

Substantially the same procedure as in Reference Example 1 was repeated using 1.60 g (4.52 mmol) of Compound 123 obtained in Reference Example 120 in place of Compound B. Then, the resultant crude crystals were recrystallized from ethyl acetate to give 1.47 g (yield 88%) of Compound 124 as pale green needles.

Melting Point: 185.3-185.7 °C

Elemental Analysis: $C_{20}H_{24}N_4O_3$			
Calcd. (%):	C, 65.20;	H, 6.56;	N, 15.21
Found (%):	C, 65.28;	H, 6.85;	N, 15.18

IR (KBr) ν_{max} (cm^{-1}): 1693, 1666, 1515, 1248

NMR (270MHz; $CDCl_3$) δ (ppm): 7.74(1H, d, J=15.8Hz), 7.52(2H, d, J=8.6Hz), 6.92(2H, d, J=8.6Hz), 6.77 (1H, d, J=15.8Hz), 4.21(2H, q, J=6.9Hz), 4.12-4.01 (4H, m), 4.04(3H, s), 1.44(3H, t, J=6.9Hz), 1.38 (3H, t, J=7.6Hz), 1.26(3H, t, J=6.9Hz)

Reference Example 122

(E)-1,3-Diethyl-8-(4-propoxystyryl)xanthine (Compound 125)

Substantially the same procedure as in Reference Example 70 was repeated using 3.00 g (15.1 mmol) of 5,6-diamino-1,3-diethyluracil and 3.43 g (16.6 mmol) of 4-propoxycinnamic acid. Then, the resultant crude crystals were recrystallized from dioxane/water to give 3.02 g (yield 54%) of Compound 125 as pale yellow needles.

Melting Point: >270 °C

Elemental Analysis: $C_{20}H_{24}N_4O_3$			
Calcd. (%):	C, 65.20;	H, 6.56;	N, 15.21
Found (%):	C, 64.91;	H, 6.79;	N, 15.14

IR (KBr) ν_{max} (cm^{-1}): 1695, 1656, 1515, 1250

NMR (270MHz; DMSO-d_6) δ (ppm): 13.38(1H, brs), 7.59 (1H, d, J=16.5Hz), 7.55(2H, d, J=8.6Hz), 6.97(2H, d, J=8.6Hz), 6.87(1H, d, J=16.5Hz), 4.07(2H, q, J=7.3Hz), 4.00-3.90(4H, m), 1.81-1.67(2H, m), 1.26 (3H, t, J=6.9Hz), 1.14(3H, t, J=6.9Hz), 0.98(3H, t, J=7.3Hz)

Reference Example 123

(E)-1,3-Diethyl-7-methyl-8-(4-propoxystyryl)xanthine (Compound 126)

Substantially the same procedure as in Reference Example 1 was repeated using 1.70 g (4.61 mmol) of Compound 125 obtained in Reference Example 122 in place of Compound B. Then, the resultant crude crystals were recrystallized from hexane/ethyl acetate to give 1.37 g (yield 78%) of Compound 126 as pale yellow needles.

Melting Point: 155.7-156.5 °C

Elemental Analysis: $C_{21}H_{26}N_4O_3$			
Calcd. (%):	C, 65.92;	H, 6.85;	N, 14.65
Found (%):	C, 65.72;	H, 7.05;	N, 14.59

IR (KBr) ν_{max} (cm^{-1}): 1696, 1665, 1513, 1246

NMR (270MHz; $CDCl_3$) δ (ppm): 7.74(1H, d, J=15.8Hz), 7.52(2H, d, J=8.6Hz), 6.92(2H, d, J=8.6Hz), 6.77 (1H, d, J=15.8Hz), 4.21(2H, q, J=6.9Hz), 4.09(2H, q, J=6.9Hz), 4.04(3H, s), 3.97(2H, t, J=6.6Hz), 1.90-1.77(2H, m), 1.38-(3H, t, J=6.9Hz), 1.26(3H, t, J=6.9Hz), 1.05(3H, t, J=7.3Hz)

Reference Example 124

(E)-1,3-Diethyl-8-(3-fluorostyryl)xanthine (Compound 127)

Substantially the same procedure as in Reference Example 70 was repeated using 3.00 g (15.1 mmol) of 5,6-diamino-1,3-diethyluracil and 2.77 g (16.7 mmol) of 3-fluorocinnamic acid. Then, the resultant crude crystals were recrystallized from dioxane/water to give 1.96 g (yield 40%) of Compound 127 as a pale yellow powder.

Melting Point: >270 °C

Elemental Analysis: $C_{17}H_{17}FN_4O_2$			
Calcd. (%):	C, 62.19;	H, 5.22;	N, 17.06
Found (%):	C, 61.90;	H, 5.21;	N, 17.15

IR (KBr) ν_{max} (cm^{-1}): 1692, 1622, 1501

NMR (270MHz; CF_3COOD) δ (ppm): 11.6(1H, brs), 8.05(1H, d, J=16.5Hz), 7.56-7.46(2H, m), 7.38(1H, d, J=9.2Hz), 7.29-7.22(1H, m), 7.19(1H, d, J=16.5Hz), 4.43-4.03(4H, m), 1.52(3H, t, J=7.3Hz), 1.41(3H, t, J=6.9Hz)

Reference Example 125

(E)-1,3-Diethyl-8-(3-fluorostyryl)-7-methylxanthine (Compound 128)

Substantially the same procedure as in Reference Example 1 was repeated using 1.80 g (5.49 mmol) of Compound 127 obtained in Reference Example 124 in place of Compound B. Then, the resultant crude crystals were recrystallized from toluene/cyclohexane to give 1.04 g (yield 55%) of Compound 128 as white needles.

Melting Point: 178.2-179.4 °C

Elemental Analysis: $C_{18}H_{19}FN_4O_2 \cdot 0.25H_2O$			
Calcd. (%):	C, 62.33;	H, 5.67;	N, 16.15
Found (%):	C, 62.19;	H, 5.63;	N, 16.26

IR (KBr) ν_{max} (cm^{-1}): 1694, 1650

NMR (270MHz; DMSO-d_6) δ (ppm): 7.75(1H, dd, J=10.1, 2.0Hz), 7.66(1H, d, J=15.8Hz), 7.63-7.60-(1H, m), 7.50-7.42(1H, m), 7.44(1H, d, J=15.8Hz), 7.19(1H, dt, J=2.0, 8.3Hz), 4.10-4.05(2H, m), 4.05(3H, s), 3.92(2H, q, J=7.0Hz), 1.26(3H, t, J=7.1Hz), 1.13 (3H, t, J=7.0Hz)

Reference Example 126

(E)-8-(3,5-Dimethoxystyryl)-1,3-diethylxanthine (Compound 129)

Substantially the same procedure as in Reference Example 70 was repeated using 3.00 g (15.1 mmol) of 5,6-diamino-1,3-diethyluracil and 3.48 g (16.7 mmol) of 3,5-dimethoxy-cinnamic acid. Then, the resultant crude crystals were recrystallized from ethanol/water to give 2.74 g (yield 49%) of Compound 129 as a white powder.

Melting Point: >270 °C

Elemental Analysis: $C_{19}H_{22}N_4O_4 \cdot 0.5H_2O$			
Calcd. (%):	C, 60.15;	H, 6.11;	N, 14.77
Found (%):	C, 60.41;	H, 6.15;	N, 15.02

IR (KBr) ν_{max} (cm^{-1}): 1686, 1638, 1587

NMR (270MHz; DMSO-d_6) δ (ppm): 7.57(1H, d, J=16.5Hz), 7.07(1H, d, J=16.5Hz), 6.79(2H, d, J=2.0Hz), 6.50 (1H, t, J=2.0Hz), 4.06(2H, q, J=7.0Hz), 3.94(2H, q, J=6.9Hz), 3.79(6H,s), 1.26(3H, t, J=7.0Hz), 1.14(3H, t, J=6.9Hz)

Reference Example 127

(E)-8-(3,5-Dimethoxystyryl)-1,3-diethyl-7-methylxanthine (Compound 130)

Substantially the same procedure as in Reference Example 1 was repeated using 3.00 g (8.11 mmol) of Compound 129 obtained in Reference Example 126 in place of Compound B. Then, the resultant crude crystals were recrystallized from toluene/cyclohexane to give 2.28 g (yield 73%) of Compound 130 as yellow needles.

Melting Point: 184.2-185.3 °C

Elemental Analysis: $C_{20}H_{24}N_4O_4$			
Calcd. (%):	C, 62.49;	H, 6.29;	N, 14.57
Found (%):	C, 62.66;	H, 6.48;	N, 14.65

IR (KBr) ν_{max} (cm^{-1}): 1690, 1659, 1595

NMR (270MHz; DMSO-d_6) δ (ppm): 7.60(1H, d, J=15.7Hz), 7.35(1H, d, J=15.7Hz), 6.98(2H, d, J=2.2Hz), 6.51 (1H, t, J=2.2Hz), 4.11-4.01(2H, m), 4.05(3H, s), 3.92(2H, q, J=7.0Hz), 3.80(6H, s), 1.26(3H, t, J=7.1Hz), 1.13(3H, t, J=7.0Hz)

Reference Example 128

(E)-8-(3-Chlorostyryl)-1,3-diethylxanthine (Compound 131)

Substantially the same procedure as in Reference Example 70 was repeated using 3.50 g (17.7 mmol) of 5,6-diamino-1,3-diethyluracil and 3.55 g (19.4 mmol) of 3-chlorocinnamic acid. Then, the resultant crude crystals were recrystallized from dioxane/water to give 2.57 g (yield 42%) of Compound 131 as white plates.

Melting Point: >280 °C

Elemental Analysis: $C_{17}H_{17}ClN_4O_2$			
Calcd. (%):	C, 59.22;	H, 4.97;	N, 16.25
Found (%):	C, 59.12;	H, 5.01;	N, 16.30

IR (KBr) ν_{max} (cm^{-1}): 1689, 1640, 1490
NMR (270MHz; CF_3COOD) δ (ppm): 8.35(1H, d, J=16.4Hz), 8.01(1H, s), 7.52-7.36(3H, m), 7.14(1H, d, J=16.4Hz), 4.37-4.23(4H, m), 1.45(3H, t, J=6.8Hz), 1.34(3H, t, J=6.9Hz)

Reference Example 129

(E)-8-(3-Chlorostyryl)-1,3-diethyl-7-methylxanthine (Compound 132)

Substantially the same procedure as in Reference Example 1 was repeated using 3.00 g (8.72 mmol) of Compound 131 obtained in Reference Example 128 in place of Compound B. Then, the resultant crude crystals were recrystallized from ethanol/water to give 1.41 g (yield 45%) of Compound 132 as a pale yellow powder.

Melting Point: 134.0-134.4 °C

Elemental Analysis: $C_{18}H_{19}ClN_4O_2 \cdot H_2O$			
Calcd. (%):	C, 57.37;	H, 5.62;	N, 14.87
Found (%):	C, 57.67;	H, 5.51;	N, 14.92

IR (KBr) ν_{max} (cm^{-1}): 1688, 1656, 1545
NMR (270MHz; DMSO-d_6) δ (ppm): 7.98(1H, s), 7.72(1H, t, J=2.0Hz), 7.63(1H, d, J=15.8Hz), 7.49-7.39(3H, m), 4.11-4.03(2H, m), 4.05(3H, s), 3.92(2H, q, J=6.9Hz), 1.26(3H, t, J=6.9Hz), 1.13(3H, t, J=6.9Hz)

Reference Example 130

(E)-1,3-Diethyl-8-(α-methylstyryl)xanthine (Compound 133)

Substantially the same procedure as in Reference Example 70 was repeated using 2.00 g (10.1 mmol) of 5,6-diamino-1,3-diethyluracil and 1.80 g (11.1 mmol) of α-methylcinnamic acid. Then, the resultant crude crystals were recrystallized from ethanol/water to give 1.63 g (yield 50%) of Compound 133 as white needles.

Melting Point: 250.8-252.0 °C

Elemental Analysis: $C_{18}H_{20}N_4O_2$			
Calcd. (%):	C, 66.65;	H, 6.21;	N, 17.27
Found (%):	C, 66.62;	H, 6.30;	N, 17.31

IR (KBr) ν_{max} (cm^{-1}): 1696, 1657, 1493
NMR (270MHz; DMSO-d_6) δ (ppm): 13.44(1H, brs), 7.61 (1H, d, J=1.3Hz), 7.49-7.30(6H, m), 4.07(2H, q, J=7.0Hz), 3.95(2H, q, J=6.9Hz), 2.31(3H, d, J=1.3Hz), 1.26-(3H, t, J=7.0Hz), 1.14(3H, t, J=6.9Hz)

Reference Example 131

(E)-1,3-Diethyl-7-methyl-8-(α-methylstyryl)xanthine (Compound 134)

Substantially the same procedure as in Reference Example 1 was repeated using 1.00 g (3.09 mmol) of Compound 133 obtained in Reference Example 130 in place of Compound B. Then, the resultant crude crystals were recrystallized from ethanol/2-propanol to give 800 mg (yield 77%) of Compound 134 as white

needles.
Melting Point: 137.2-139.3 • C

Elemental Analysis: $C_{19}H_{22}N_4O_2$			
Calcd. (%):	C, 67.44;	H, 6.55;	N, 16.56
Found (%):	C, 67.01;	H, 6.73;	N, 16.62

IR (KBr) ν_{max} (cm^{-1}): 1699, 1654, 1537
NMR (270MHz; DMSO-d_6) δ (ppm): 7.52-7.32(5H, m), 7.00 (1H, d, J=1.3Hz), 4.04(2H, q, J=7.2Hz), 4.00(3H, s), 3.94(2H, q, J=6.9Hz), 2.29(3H, d, J=1.3Hz), 1.24-(3H, t, J=7.2Hz), 1.13(3H, t, J=6.9Hz)

Reference Example 132

(E)-1,3-Diethyl-8-(4-trifluoromethylstyryl)xanthine (Compound 135)

Substantially the same procedure as in Reference Example 70 was repeated using 2.20 g (11.2 mmol) of 5,6-diamino-1,3-diethyluracil and 2.66 g (12.3 mmol) of 4-trifluoromethyl-cinnamic acid. Then, the resultant crude crystals were recrystallized from dioxane/water to give 2.09 g (yield 49%) of Compound 135 as a white powder.
Melting Point: >280 • C

Elemental Analysis: $C_{18}H_{17}F_3N_4O_2$			
Calcd. (%):	C, 57.14;	H, 4.53;	N, 14.81
Found (%):	C, 57.25;	H, 4.51;	N, 14.82

IR (KBr) ν_{max} (cm^{-1}): 1696, 1654, 1637, 1324
NMR (270MHz; DMSO-d_6) δ (ppm): 7.86(2H, d, J=8.1Hz), 7.76(2H, d, J=8.1Hz), 7.70(1H, d, J=16.5Hz), 7.20 (1H, d, J=16.5Hz), 4.07(2H, q, J=7.1Hz), 3.94-(2H, q, J=7.0Hz), 1.26(3H, t, J=7.1Hz), 1.14(3H, t, J=7.0Hz)

Reference Example 133

(E)-1,3-Diethyl-7-methyl-8-(4-trifluoromethylstyryl)xanthine (Compound 136)

Substantially the same procedure as in Reference Example 1 was repeated using 1.30 g (3.44 mmol) of Compound 135 obtained in Reference Example 132 in place of Compound B. Then, the resultant crude crystals were recrystallized from toluene/cyclohexane to give 990 mg (yield 73%) of Compound 136 as yellow needles.
Melting Point: 207.8-209.0 • C

Elemental Analysis: $C_{19}H_{19}F_3N_4O_2$			
Calcd. (%):	C, 58.16;	H, 4.88;	N, 14.28
Found (%):	C, 58.22;	H, 4.84;	N, 14.32

IR (KBr) ν_{max} (cm^{-1}): 1700, 1667, 1325
NMR (270MHz; DMSO-d_6) δ (ppm): 8.03(2H, d, J=8.3Hz), 7.76(2H, d, J=8.3Hz), 7.73(1H, d, J=15.8Hz), 7.53 (1H, d, J=15.8Hz), 4.11-4.03(2H, m), 4.09(3H, s), 3.92(2H, q, J=7.0Hz), 1.27(3H, t, J=6.9Hz), 1.13(3H, t, J=7.0Hz)

Reference Example 134

(E)-1,3-Diethyl-8-(α-fluorostyryl)xanthine (Compound 137)

Substantially the same procedure as in Reference Example 70 was repeated using 1.08 g (5.47 mmol) of 5,6-diamino-1,3-diethyluracil and 1.00 g (6.02 mmol) of α-fluorocinnamic acid. Then, the resultant crude crystals were recrystallized from dioxane/water to give 1.04 g (yield 58%) of Compound 137 as white plates.

Melting Point: >280 • C

Elemental Analysis: $C_{17}H_{17}FN_4O_2$			
Calcd. (%):	C, 62.19;	H, 5.22;	N, 17.06
Found (%):	C, 62.28;	H, 5.22;	N, 17.07

IR (KBr) ν_{max} (cm^{-1}): 1695, 1644, 1506

NMR (270MHz; DMSO-d_6) δ (ppm): 7.68(2H, d, J=6.9Hz), 7.47-7.35(3H, m), 6.93(1H, d, J=36.3Hz), 4.06(2H, q, J=6.9Hz), 3.94(2H, q, J=7.0Hz), 1.26(3H, t, J=6.9Hz), 1.14(3H, t, J=7.0Hz)

Reference Example 135

(E)-1,3-Diethyl-8-(α-fluorostyryl)-7-methylxanthine (Compound 138)

Substantially the same procedure as in Reference Example 1 was repeated using 800 mg (2.44 mmol) of Compound 137 obtained in Reference Example 134 in place of Compound B. Then, the resultant crude crystals were recrystallized from toluene/cyclohexane to give 550 mg (yield 66%) of Compound 138 as a white powder.

Melting Point: 153.5-155.5 • C

Elemental Analysis: $C_{18}H_{19}FN_4O_2$			
Calcd. (%):	C, 63.15;	H, 5.59;	N, 16.36
Found (%):	C, 63.25;	H, 5.66;	N, 16.44

IR (KBr) ν_{max} (cm^{-1}): 1696, 1662, 1539

NMR (270MHz; $CDCl_3$) δ (ppm): 7.68-7.65(2H, m), 7.47-7.31(3H, m), 6.89(1H, d, J=39.3Hz), 4.13-4.05(2H, m), 4.21(3H, s), 4.09(2H, q, J=7.1Hz), 1.37(3H, t, J=7.1Hz), 1.27(3H, t, J=7.1Hz)

Reference Example 136

(E)-1,3-Diethyl-8-(3-methoxystyryl)xanthine (Compound 139)

Substantially the same procedure as in Reference Example 70 was repeated using 2.50 g (12.6 mmol) of 5,6-diamino-1,3-diethyluracil and 2.48 g (13.9 mmol) of 3-methoxycinnamic acid. Then, the resultant crude crystals were recrystallized from dimethylformamide/water to give 2.10 g (yield 49%) of Compound 139 as a white powder.

Melting Point: 270.6-272.5 • C

Elemental Analysis: $C_{18}H_{20}N_4O_3$			
Calcd. (%):	C, 63.52;	H, 5.92;	N, 16.46
Found (%):	C, 63.20;	H, 6.01;	N, 16.34

IR (KBr) ν_{max} (cm^{-1}): 1686, 1634, 1500

NMR (270MHz; DMSO-d_6) δ (ppm): 7.61(1H, d, J=16.4Hz), 7.34(1H, t, J=7.9Hz), 7.20-7.18(2H, m), 7.07(1H, d, J=16.4Hz), 6.92(1H, d, J=8.6Hz), 4.06(2H, q, J=7.0Hz), 3.94(2H, q, J=6.8Hz), 1.26(3H, t, J=7.0Hz), 1.14(3H, t, J=6.8Hz)

Reference Example 137

(E)-1,3-Diethyl-8-(3-methoxystyryl)-7-methylxanthine (Compound 140)

Substantially the same procedure as in Reference Example 1 was repeated using 1.70 g (5.00 mmol) of Compound 139 obtained in Reference Example 136 in place of Compound B. Then, the resultant crude crystals were recrystallized from toluene/cyclohexane to give 1.10 g (yield 62%) of Compound 140 as pale yellow needles.

Melting Point: 153.4-154.8 °C

Elemental Analysis: $C_{19}H_{22}N_4O_3$			
Calcd. (%):	C, 64.39;	H, 6.26;	N, 15.81
Found (%):	C, 64.34;	H, 6.38;	N, 15.82

IR (KBr) ν_{max} (cm^{-1}): 1692, 1656, 1541

NMR (270MHz; DMSO-d_6) δ (ppm): 7.64(1H, d, J=15.8Hz), 7.40-7.30(4H, m), 6.97-6.92(1H, m), 4.31-4.05(2H, m), 4.05(3H, s), 3.92(2H, q, J=7.0Hz), 1.26(3H, t, J=7.1Hz), 1.13(3H, t, J=7.0Hz)

Reference Example 138

(E)-8-(4-Bromostyryl)-1,3-diethylxanthine (Compound 141)

Substantially the same procedure as in Reference Example 70 was repeated using 2.20 g (11.1 mmol) of 5,6-diamino-1,3-diethyluracil and 2.78 g (12.2 mmol) of 4-bromocinnamic acid. Then, the resultant crude crystals were recrystallized from tetrahydrofuran/water to give 930 mg (yield 22%) of Compound 141 as yellow columns.

Melting Point: >270 °C

Elemental Analysis: $C_{17}H_{17}BrN_4O_2$			
Calcd. (%):	C, 52.46;	H, 4.40;	N, 14.39
Found (%):	C, 52.41;	H, 4.28;	N, 14.43

IR (KBr) ν_{max} (cm^{-1}): 1686, 1619, 1496

NMR (270MHz; DMSO-d_6) δ (ppm): 7.63-7.18(4H, m), 7.60 (1H, d, J=16.2Hz), 7.07(1H, d, J=16.2Hz), 4.06(2H, q, J=6.9Hz), 3.94(2H, q, J=6.8Hz), 1.26-(3H, t, J=6.9Hz), 1.14(3H, t, J=6.8Hz)

Reference Example 139

(E)-8-(4-Bromostyryl)-1,3-diethyl-7-methylxanthine (Compound 142)

Substantially the same procedure as in Reference Example 1 was repeated using 1.80 g (4.63 mmol) of Compound 141 obtained in Reference Example 138 in place of Compound B. Then, the resultant crude

crystals were recrystallized from toluene/ethanol to give 660 mg (yield 35%) of Compound 142 as pale yellow needles.

Melting Point: 198.5-198.9 • C

Elemental Analysis: $C_{18}H_{19}BrN_4O_2 \cdot 0.25H_2O$			
Calcd. (%):	C, 53.02;	H, 4.82;	N, 13.74
Found (%):	C, 53.09;	H, 4.62;	N, 13.79

IR (KBr) ν_{max} (cm^{-1}): 1691, 1662, 1543

NMR (270MHz; DMSO-d_6) δ (ppm): 7.78(2H, d, J=7.6Hz), 7.67-7.61(3H, m), 7.41(1H, d, J=16.2Hz), 4.11-4.04 (2H, m), 4.04(3H, s), 3.92(2H, q, J=6.7Hz), 1.26 (3H, t, J=6.8Hz), 1.13(3H, t, J=6.7Hz)

Reference Example 140

(E)-1,3-Diethyl-8-(3-trifluoromethoxystyryl)xanthine (Compound 143)

Substantially the same procedure as in Reference Example 70 was repeated using 1.00 g (5.05 mmol) of 5,6-diamino-1,3-diethyluracil and 1.29 g (5.56 mmol) of 3-trifluoromethoxy-cinnamic acid. Then, the resultant crude crystals were recrystallized from dioxane/water to give 1.19 g (yield 60%) of Compound 143 as white needles.

Melting Point: 266.4-267.3 • C

Elemental Analysis: $C_{18}H_{17}F_3N_4O_3$			
Calcd. (%):	C, 54.83;	H, 4.34;	N, 14.21
Found (%):	C, 54.79;	H, 4.22;	N, 14.20

IR (KBr) ν_{max} (cm^{-1}): 1697, 1658, 1500, 1262

NMR (270MHz; DMSO-d_6) δ (ppm): 13.57(1H, brs), 7.67 (1H, d, J=16.5Hz), 7.66(1H, d, J=7.9Hz), 7.63(1H, s), 7.55(1H, t, J=7.9Hz), 7.34(1H, d, J=7.9Hz), 7.14(1H, d, J=16.5Hz), 4.07(2H, q, J=6.9Hz), 3.94 (2H, q, J=6.9Hz), 1.27(3H, t, J=6.9Hz), 1.14(3H, t, J=6.9Hz)

Reference Example 141

(E)-1,3-Diethyl-7-methyl-8-(3-trifluoromethoxystyryl)xanthine (Compound 144)

Substantially the same procedure as in Reference Example 1 was repeated using 700 mg (1.78 mmol) of Compound 143 obtained in Reference Example 140 in place of Compound B. Then, the resultant crude crystals were recrystallized from ethyl acetate to give 329 mg (yield 45%) of Compound 144 as white needles.

Melting Point: 178.7-179.3 • C

Elemental Analysis: $C_{19}H_{19}F_3N_4O_3$			
Calcd. (%):	C, 55.88;	H, 4.69;	N, 13.72
Found (%):	C, 56.27;	H, 4.68;	N, 13.67

IR (KBr) ν_{max} (cm^{-1}): 1694, 1660, 1265, 1213

NMR (270MHz; $CDCl_3$) δ (ppm): 7.77(1H, d, J=15.8Hz), 7.53-7.20(4H, m), 6.93(1H, d, J=15.8Hz), 4.21(2H, q, J=6.9Hz), 4.09(2H, q, J=6.9Hz), 4.08(3H, s), 1.38(3H, t, J=6.9Hz), 1.27(3H, t, J=6.9Hz)

Reference Example 142

(E)-1,3-Diethyl-8-(4-methoxymethoxystyryl)xanthine (Compound 145)

Substantially the same procedure as in Reference Example 70 was repeated using 4.00 g (20.2 mmol) of 5,6-diamino-1,3-diethyluracil and 4.62 g (22.2 mmol) of 4-methoxymethoxy-cinnamic acid. Then, the resultant crude crystals were recrystallized from dioxane/water to give 4.80 g (yield 64%) of Compound 145 as pale yellow needles.

Melting Point: 270.2-271.4 • C

Elemental Analysis: $C_{19}H_{22}N_4O_4$			
Calcd. (%):	C, 61.61;	H, 5.98;	N, 15.13
Found (%):	C, 61.97;	H, 5.98;	N, 15.0

IR (KBr) ν_{max} (cm^{-1}): 1695, 1641, 1510, 1238

NMR (270MHz; DMSO-d_6) δ (ppm): 13.40(1H, brs), 7.60 (1H, d, J = 16.5Hz), 7.57(2H, d, J = 8.6Hz), 7.06(2H, d, J = 8.6Hz), 6.90(1H, d, J = 16.5Hz), 5.23(2H, s), 4.07-(2H, q, J = 6.9Hz), 3.94(2H, q, J = 6.9Hz), 3.39 (3H, s), 1.26(3H, t, J = 6.9Hz), 1.14(3H, t, J = 6.9Hz)

Reference Example 143

(E)-1,3-Diethyl-8-(4-methoxymethoxystyryl)-7-methylxanthine (Compound 146)

Substantially the same procedure as in Reference Example 1 was repeated using 3.50 g (9.45 mmol) of Compound 145 obtained in Reference Example 142 in place of Compound B. Then, the resultant crude crystals were recrystallized from hexane/ethyl acetate to give 3.39 g (yield 93%) of Compound 146 as pale yellow plates.

Melting Point: 163.9-164.7 • C

Elemental Analysis: $C_{20}H_{24}N_4O_4$			
Calcd. (%):	C, 62.49;	H, 6.29;	N, 14.57
Found (%):	C, 62.21;	H, 6.27;	N, 14.58

IR (KBr) ν_{max} (cm^{-1}): 1688, 1651, 1510, 1238

NMR (270MHz; $CDCl_3$) δ (ppm): 7.75(1H, d, J = 15.8Hz), 7.53(2H, d, J = 8.6Hz), 7.07(2H, d, J = 8.6Hz), 6.79 (1H, d, J = 15.8Hz), 5.21(2H, s), 4.21(2H, q, J = 6.9Hz), 4.09(2H, q, J = 6.9Hz), 4.05(3H, s), 3.50 (3H, s), 1.38(3H, t, J = 6.9Hz), 1.26(3H, t, J = 6.9Hz)

Reference Example 144

(E)-8-(4-Butoxystyryl)-1,3-diethylxanthine (Compound 147)

Substantially the same procedure as in Reference Example 70 was repeated using 3.00 g (15.1 mmol) of 5,6-diamino-1,3-diethyluracil and 3.67 g (16.7 mmol) of 4-butoxycinnamic acid. Then, the resultant crude crystals were recrystallized from dioxane/water to give 3.04 g (yield 53%) of Compound 147 as pale yellow needles.

Melting Point: 257.9-261.3 • C

Elemental Analysis: $C_{21}H_{26}N_4O_3$			
Calcd. (%):	C, 65.95;	H, 6.85;	N, 14.65
Found (%):	C, 65.90;	H, 7.21;	N, 14.60

IR (KBr) ν_{max} (cm^{-1}): 1695, 1645, 1515, 1248
NMR (270MHz; DMSO-d_6) δ (ppm): 13.32(1H, brs), 7.59 (1H, d, J=16.5Hz), 7.55(2H, d, J=8.9Hz), 6.97(2H, d, J=8.9Hz), 6.87(1H, d, J=16.5Hz), 4.10-3.90(6H, m), 1.76-1.66(2H, m), 1.51-1.40(2H, m), 1.26(3H, t, J=6.9Hz), 1.14-(3H, t, J=6.9Hz), 0.94(3H, t, J=7.3Hz)

Reference Example 145

(E)-8-(4-Butoxystyryl)-1,3-diethyl-7-methylxanthine (Compound 148)

Substantially the same procedure as in Reference Example 1 was repeated using 1.50 g (3.92 mmol) of Compound 147 obtained in Reference Example 144 in place of Compound B. Then, the resultant crude crystals were recrystallized from hexane/ethyl acetate to give 982 mg (yield 63%) of Compound 148 as pale yellow needles.
Melting Point: 123.4-123.6 °C

Elemental Analysis: $C_{22}H_{28}N_4O_3$			
Calcd. (%):	C, 66.65;	H, 7.11;	N, 14.13
Found (%):	C, 66.81;	H, 7.31;	N, 14.01

IR (KBr) ν_{max} (cm^{-1}): 1693, 1665, 1513, 1251
NMR (270MHz; $CDCl_3$) δ (ppm): 7.74(1H, d, J=15.8Hz), 7.52(2H, d, J=8.9Hz), 6.92(2H, d, J=8.9Hz), 6.76 (1H, d, J=15.8Hz), 4.21(2H, q, J=6.9Hz), 4.09(2H, q, J=6.9Hz), 4.04(3H, s), 4.02(2H, q, J=6.6Hz), 1.84-1.74(2H, m), 1.58-1.44(2H, m), 1.38(3H, t, J=6.9Hz), 1.26(3H, t, J=6.9Hz), 0.99(3H, t, J=7.3Hz)

Reference Example 146

(E)-1,3-Diethyl-8-(4-fluorostyryl)xanthine (Compound 149)

Substantially the same procedure as in Reference Example 70 was repeated using 2.50 g (12.6 mmol) of 5,6-diamino-1,3-diethyluracil and 2.31 g (13.9 mmol) of 4-fluorocinnamic acid. Then, the resultant crude crystals were recrystallized from tetrahydrofuran/water to give 2.00 g (yield 51%) of Compound 149 as colorless columns.
Melting Point: >270 °C

Elemental Analysis: $C_{17}H_{17}FN_4O_2$			
Calcd. (%):	C, 62.19;	H, 5.22;	N, 17.06
Found (%):	C, 62.02;	H, 5.12;	N, 17.02

IR (KBr) ν_{max} (cm^{-1}): 1689, 1560, 1508
NMR (270MHz; DMSO-d_6) δ (ppm): 8.06(1H, d, J=16.3Hz), 7.72(2H, dd, J=8.6, 5.2Hz), 7.21(2H, t, J=8.6Hz), 7.10(1H, d, J=16.3Hz), 4.43-4.30(4H, m), 1.53(3H, t, J=7.2Hz), 1.41(3H, t, J=7.2Hz)

Reference Example 147

(E)-1,3-Diethyl-8-(4-fluorostyryl)-7-methylxanthine (Compound 150)

Substantially the same procedure as in Reference Example 1 was repeated using 1.80 g (5.18 mmol) of Compound 149 obtained in Reference Example 146 in place of Compound B. Then, the resultant crude crystals were recrystallized from toluene/cyclohexane to give 510 mg (yield 29%) of Compound 150 as white needles.

Melting Point: 182.0-182.5 °C

Elemental Analysis: $C_{18}H_{19}FN_4O_2$			
Calcd. (%):	C, 63.15;	H, 5.59;	N, 16.36
Found (%):	C, 63.18;	H, 5.61;	N, 16.40

IR (KBr) ν_{max} (cm^{-1}): 1687, 1654, 1514

NMR (270MHz; DMSO-d_6) δ (ppm): 7.88(2H, dd, J=8.1, 5.8Hz), 7.67(1H, d, J=15.8Hz), 7.41-7.24(3H, m), 4.11-4.03(2H, m), 4.03(3H, s), 3.92(2H, q, J=6.8Hz), 1.26(3H, t, J=6.9Hz), 1.13(3H, t, J=6.8Hz)

Reference Example 148

(E)-1,3-Diethyl-8-(4-methylstyryl)xanthine (Compound 151)

Substantially the same procedure as in Reference Example 70 was repeated using 3.00 g (15.1 mmol) of 5,6-diamino-1,3-diethyluracil and 2.70 g (16.7 mmol) of 4-methylcinnamic acid. Then, the resultant crude crystals were recrystallized from dioxane to give 2.64 g (yield 54%) of Compound 151 as pale yellow needles.

Melting Point: >280 °C

Elemental Analysis: $C_{18}H_{20}N_4O_2$			
Calcd. (%):	C, 66.65;	H, 6.21;	N, 17.27
Found (%):	C, 66.53;	H, 6.27;	N, 17.14

IR (KBr) ν_{max} (cm^{-1}): 1692, 1644, 1518, 1490

NMR (270MHz; DMSO-d_6) δ (ppm): 13.53(1H, brs), 7.62 (1H, d, J=16.5Hz), 7.52(2H, d, J=7.9Hz), 7.24(2H, d, J=7.9Hz), 6.98(1H, d, J=16.5Hz), 4.07(2H, q, J=6.9Hz), 3.94(2H, q, J=6.9Hz), 2.33(3H, s), 1.26 (3H, t, J=6.9Hz), 1.14(3H, t, J=6.9Hz)

Reference Example 149

(E)-1,3-Diethyl-7-methyl-8-(4-methylstyryl)xanthine (Compound 152)

Substantially the same procedure as in Reference Example 1 was repeated using 1.50 g (4.62 mmol) of Compound 151 obtained in Reference Example 148 in place of Compound B. Then, the resultant crude crystals were recrystallized from dioxane/water to give 1.39 g (yield 89%) of Compound 152 as yellow needles.

Melting Point: 170.8-171.5 °C

Elemental Analysis: $C_{19}H_{22}N_4O_2$			
Calcd. (%):	C, 67.44;	H, 6.55;	N, 16.56
Found (%):	C, 67.58;	H, 6.65;	N, 16.68

IR (KBr) ν_{max} (cm^{-1}): 1687, 1650, 1542, 1516

NMR (270MHz; $CDCl_3$) δ (ppm): 7.77(1H, d, J=15.8Hz), 7.48(2H, d, J=8.3Hz), 7.21(2H, d, J=8.3Hz), 6.87 (1H, d, J=15.8Hz), 4.22(2H, q, J=6.9Hz), 4.09(2H, q, J=6.9Hz), 4.05(3H, s), 2.39(3H, s), 1.38(3H, t, J=6.9Hz), 1.26(3H, t, J=6.9Hz)

Reference Example 150

(E)-8-[3,5-Bis(trifluoromethyl)styryl]-1,3-diethylxanthine (Compound 153)

Substantially the same procedure as in Reference Example 70 was repeated using 3.00 g (15.1 mmol) of 5,6-diamino-1,3-diethyluracil and 4.73 g (16.7 mmol) of 3,5-bis(trifluoromethyl)cinnamic acid. Then, the resultant crude crystals were recrystallized from dioxane to give 4.09 g (yield 61%) of Compound 153 as pale yellow needles.

Melting Point: >280 °C

Elemental Analysis: $C_{19}H_{16}F_6N_4O_2$			
Calcd. (%):	C, 51.13;	H, 3.61;	N, 12.55
Found (%):	C, 50.96;	H, 3.40;	N, 12.52

IR (KBr) ν_{max} (cm^{-1}): 1694, 1649, 1495, 1287

NMR (270MHz; DMSO-d_6) δ (ppm): 13.75(1H, brs), 8.35 (2H, s), 8.05(1H, s), 7.80(1H, d, J=16.5Hz), 7.40 (1H, d, J=16.5Hz), 4.08(2H, q, J=6.9Hz), 3.94(2H, q, J=6.9Hz), 1.27(3H, t, J=6.9Hz), 1.14(3H, t, J=6.9Hz)

Reference Example 151

(E)-8-[3,5-Bis(trifluoromethyl)styryl]-1,3-diethyl-7-methylxanthine (Compound 154)

Substantially the same procedure as in Reference Example 1 was repeated using 2.00 g (4.68 mmol) of Compound 153 obtained in Reference Example 150 in place of Compound B. Then, the resultant crude crystals were recrystallized from dioxane/water to give 1.43 g (yield 69%) of Compound 154 as pale green needles.

Melting Point: 204.9-205.1 °C

MS-EI m/e: 460(M^+)

IR (KBr) ν_{max} (cm^{-1}): 1699, 1653, 1546, 1282

NMR (270MHz; DMSO-d_6) δ (ppm): 8.55(2H, s), 8.01(1H, s), 7.85(1H, d, J=15.8Hz), 7.72(1H, d, J=15.8Hz), 4.09(3H, s), 4.08(2H, q, J=6.9Hz), 3.93(2H, q, J=6.9Hz), 1.28(3H, t, J=6.9Hz), 1.14(3H, t, J=6.9Hz)

Reference Example 152

(E)-8-(3,5-Difluorostyryl)-1,3-diethylxanthine (Compound 155)

Substantially the same procedure as in Reference Example 70 was repeated using 3.00 g (15.1 mmol) of 5,6-diamino-1,3-diethyluracil and 3.06 g (16.6 mmol) of 3,5-difluorocinnamic acid. Then, the resultant crude crystals were recrystallized from dioxane/water to give 3.30 g (yield 63%) of Compound 155 as pale yellow plates.

Melting Point: >280 °C

Elemental Analysis: $C_{17}H_{16}F_2N_4O_2$			
Calcd. (%):	C, 58.96;	H, 4.65;	N, 16.18
Found (%):	C, 58.82;	H, 4.65;	N, 16.07

IR (KBr) ν_{max} (cm^{-1}): 1686, 1634, 1589, 1489

NMR (270MHz; DMSO-d_6) δ (ppm): 13.66(1H, brs), 7.60 (1H, d, J=16.5Hz), 7.36(2H, dd, J=8.6, 2.0Hz), 7.20(1H, dt, J=9.2, 2.0Hz), 7.16(1H, d, J=16.5Hz), 4.07-(2H, q, J=6.9Hz), 3.94(2H, q, J=6.9Hz), 1.26 (3H, t, J=6.9Hz), 1.14(3H, t, J=6.9Hz)

Reference Example 153

(E)-8-(3,5-Difluorostyryl)-1,3-diethyl-7-methylxanthine(Compound 156)

Substantially the same procedure as in Reference Example 1 was repeated using 2.00 g (5.78 mmol) of Compound 155 obtained in Reference Example 152 in place of Compound B. Then, the resultant crude crystals were recrystallized from hexane/ethyl acetate to give 1.80 g (yield 87%) of Compound 156 as pale yellow needles.

Melting Point: 177.0-178.6 °C

MS-EI m/e: 360(M^+)

IR (KBr) ν_{max} (cm^{-1}): 1683, 1619, 1593, 1543

NMR (270MHz; $CDCl_3$) δ (ppm): 7.70(1H, d, J=15.5Hz), 7.09(2H, dd, J=8.3, 2.0Hz), 6.91(1H, d, J=15.5Hz), 6.81(1H, dt, J=8.6, 2.0Hz), 4.21(2H, q, J=6.9Hz), 4.09-(2H, q, J=6.9Hz), 4.08(3H, s), 1.38(3H, t, J=6.9Hz), 1.27(3H, t, J=6.9Hz)

Reference Example 154

(E)-1,3-Diethyl-8-(2-methoxystyryl)xanthine (Compound 157)

Substantially the same procedure as in Reference Example 70 was repeated using 2.5 g (12.6 mmol) of 5,6-diamino-1,3-diethyluracil and 2.48 g (13.9 mmol) of 2-methoxycinnamic acid. Then, the resultant crude crystals were recrystallized from tetrahydrofuran/water to give 990 mg (yield 24%) of Compound 157 as yellow grains.

Melting Point: >270 °C

Elemental Analysis: $C_{18}H_{20}N_4O_3$			
Calcd. (%):	C, 63.52;	H, 5.92;	N, 16.46
Found (%):	C, 63.28;	H, 5.86;	N, 16.43

IR (KBr) ν_{max} (cm^{-1}): 1694, 1640, 1501

NMR (270MHz; DMSO-d_6) δ (ppm): 7.85(1H, d, J=16.8Hz), 7.62(1H, d, J=7.6Hz), 7.34(1H, t, J=7.6Hz), 7.11-6.98(3H, m), 4.07(2H, q, J=7.0Hz), 3.97-3.89(2H, m), 3.89(3H, s), 1.26(3H, t, J=7.0Hz), 1.14(3H, t, J=6.9Hz)

Reference Example 155

(E)-1,3-Diethyl-8-(2-methoxystyryl)-7-methylxanthine (Compound 158)

Substantially the same procedure as in Reference Example 1 was repeated using 1.5 g (4.41 mmol) of Compound 157 obtained in Reference Example 154 in place of Compound B. Then, the resultant crude crystals were recrystallized from ethanol/water to give 800 mg (yield 51%) of Compound 158 as yellow needles.

Melting Point: 189.6-190.0 °C

Elemental Analysis: $C_{19}H_{22}N_4O_3$			
Calcd. (%):	C, 64.39;	H, 6.26;	N, 15.81
Found (%):	C, 64.18;	H, 6.25;	N, 15.77

IR (KBr) ν_{max} (cm^{-1}): 1697, 1649

NMR (270MHz; DMSO-d_6) δ (ppm): 7.94(1H, d, J=15.8Hz), 7.88(1H, dd, J=7.9, 1.5Hz), 7.41-7.34(1H, m), 7.31 (1H, d, J=15.8Hz), 7.10(1H, d, J=7.9Hz), 7.02(1H, t, J=7.4Hz), 4.11-4.02(2H, m), 4.02(3H, s), 3.96-3.90(2H, m), 3.90-(3H, s), 1.29(3H, t, J=7.2Hz), 1.13(3H, t, J=7.2Hz)

Reference Example 156

(E)-1,3-Diethyl-8-(3-nitrostyryl)xanthine (Compound 159)

Substantially the same procedure as in Reference Example 70 was repeated using 2.5 g (12.6 mmol) of 5,6-diamino-1,3-diethyluracil and 2.68 g (13.9 mmol) of 3-nitrocinnamic acid. Then, the resultant crude crystals were recrystallized from dioxane/water to give 2.01 g (yield 30%) of Compound 159 as a yellow powder.

Melting Point: >270 • C

Elemental Analysis: $C_{17}H_{17}N_5O_4 \cdot 0.25C_4H_8O_2$			
Calcd. (%):	C, 57.29;	H, 5.07;	N, 18.56
Found (%):	C, 57.38;	H, 5.06;	N, 18.63

IR (KBr) ν_{max} (cm^{-1}): 1688, 1640, 1530

NMR (270MHz; DMSO-d_6) δ (ppm): 8.42(1H, d, J=1.7Hz), 8.18(1H, dd, J=8.3, 1.7Hz), 8.12(1H, d, J=7.9Hz), 7.75(1H, d, J=16.5Hz), 7.71(1H, t, J=7.9Hz), 7.24 (1H, d, J=16.5Hz), 4.08(2H, q, J=7.0Hz), 3.94(2H, q, J=7.0Hz), 1.27(3H, t, J=7.0Hz), 1.14(3H, t, J=7.0Hz)

Reference Example 157

(E)-1,3-Diethyl-7-methyl-8-(3-nitrostyryl)xanthine (Compound 160)

Substantially the same procedure as in Reference Example 1 was repeated using 700 mg (1.97 mmol) of Compound 159 obtained in Reference Example 156 in place of Compound B. Then, the resultant crude crystals were recrystallized from acetonitrile to give 340 mg (yield 47%) of Compound 160 as a yellow powder.

Melting Point: 250.5-251.7 • C

Elemental Analysis: $C_{18}H_{19}N_5O_4$			
Calcd. (%):	C, 58.53;	H, 5.18;	N, 18.96
Found (%):	C, 58.47;	H, 5.13;	N, 18.89

IR (KBr) ν_{max} (cm^{-1}): 1699, 1666, 1524

NMR (270MHz; DMSO-d_6) δ (ppm): 8.72(1H, s), 8.25(1H, d, J=7.9Hz), 8.19(1H, d, J=7.4Hz), 7.79-(1H, d, J=15.8Hz), 7.72(1H, t, J=7.9Hz), 7.63(1H, d, J=15.8Hz), 4.12-4.05(2H, m), 4.08(3H, s), 3.93(2H, q, J=7.2Hz), 1.27(3H, t, J=7.2Hz), 1.13(3H, t, J=7.2Hz)

Reference Example 158

(E)-8-(3-Bromostyryl)-1,3-diethylxanthine (Compound 161)

Substantially the same procedure as in Reference Example 70 was repeated using 2.0 g (10.1 mmol) of 5,6-diamino-1,3-diethyluracil and 2.52 g (11.1 mmol) of 3-bromocinnamic acid. Then, the resultant crude crystals were recrystallized from tetrahydrofuran/water to give 2.01 g (yield 37%) of Compound 161 as pale green plates.

Melting Point: >270 °C

Elemental Analysis: $C_{17}H_{17}BrN_4O_2$			
Calcd. (%):	C, 52.46;	H, 4.40;	N, 14.39
Found (%):	C, 52.54;	H, 4.44;	N, 14.37

IR (KBr) ν_{max} (cm^{-1}): 1683, 1636, 1492

NMR (270MHz; CF_3COOD) δ (ppm): 7.99(1H, d, J=16.6Hz), 7.84(1H, s), 7.70(1H, d, J=7.9Hz), 7.62-(1H, d, J=7.9Hz), 7.40(1H, t, J=7.9Hz), 7.19(1H, d, J=16.6Hz), 4.40-4.30(4H, m), 1.53(3H, t, J=7.2Hz), 1.41(3H, t, J=7.2Hz)

Reference Example 159

(E)-8-(3-Bromostyryl)-1,3-diethyl-7-methylxanthine (Compound 162)

Substantially the same procedure as in Reference Example 1 was repeated using 2.5 g (6.43 mmol) of Compound 161 obtained in Reference Example 158 in place of Compound B. Then, the resultant crude crystals were recrystallized from toluene/cyclohexane to give 600 mg (yield 69%) of Compound 162 as a yellow powder.

Melting Point: 187.3-188.2 °C

Elemental Analysis: $C_{18}H_{19}BrN_4O_2$			
Calcd. (%):	C, 53.61;	H, 4.75;	N, 13.89
Found (%):	C, 53.83;	H, 4.63;	N, 13.70

IR (KBr) ν_{max} (cm^{-1}): 1694, 1654

NMR (270MHz; DMSO-d_6) δ (ppm): 8.13(1H, s), 7.76(1H, d, J=7.6Hz), 7.63(1H, d, J=15.8Hz), 7.54-(1H, d, J=8.9Hz), 7.46(1H, d, J=15.8Hz), 7.37(1H, t, J=8.2Hz), 4.11-4.03(2H, m), 4.05(3H, s), 3.92(2H, q, J=6.9Hz), 1.26(3H, t, J=6.9Hz), 1.13(3H, t, J=6.9Hz)

Reference Example 160

(E)-1,3-Diethyl-8-(3-trifluoromethylstyryl)xanthine (Compound 163)

Substantially the same procedure as in Reference Example 70 was repeated using 2.50 g (12.6 mmol) of 5,6-diamino-1,3-diethyluracil and 3.0 g (13.9 mmol) of 3-trifluoromethyl-cinnamic acid. Then, the resultant crude crystals were recrystallized from acetonitrile/water to give 2.07 g (yield 44%) of Compound 163 as white needles.

Melting Point: >270 °C

Elemental Analysis: $C_{18}H_{17}F_3N_4O_2$			
Calcd. (%):	C, 57.14;	H, 4.53;	N, 14.81
Found (%):	C, 57.15;	H, 4.47;	N, 14.65

IR (KBr) ν_{max} (cm^{-1}): 1691, 1641, 1495, 1334

NMR (270MHz; DMSO-d_6) δ (ppm): 13.65(1H, brs), 7.99-7.95(2H, m), 7.76-7.63(3H, m), 7.21(1H, d, J=16.1Hz), 4.07(2H, q, J=6.9Hz), 3.94(2H, q, J=6.7Hz), 1.27-(3H, t, J=6.9Hz), 1.14(3H, t, J=6.7Hz)

Reference Example 161

(E)-1,3-Diethyl-7-methyl-8-(3-trifluoromethylstyryl)xanthine (Compound 164)

Substantially the same procedure as in Reference Example 1 was repeated using 1.70 g (4.50 mmol) of Compound 163 obtained in Reference Example 160 in place of Compound B. Then, the resultant crude crystals were recrystallized from toluene/cyclohexane to give 1.14 g (yield 65%) of Compound 164 as a pale yellow powder.

Melting Point: 214.8-215.3 °C

Elemental Analysis: $C_{19}H_{19}F_3N_4O_2$			
Calcd. (%):	C, 58.16;	H, 4.88;	N, 14.28
Found (%):	C, 58.13;	H, 4.90;	N, 14.22

IR (KBr) ν_{max} (cm^{-1}): 1697, 1664

NMR (270MHz; DMSO-d_6) δ (ppm): 8.26(1H, s), 8.09(1H, d, J=7.4Hz), 7.75(1H, d, J=15.8Hz), 7.69-7.62(2H, m), 7.56(1H, d, J=15.8Hz), 4.12-4.00(2H, m), 4.07 (3H, s), 3.92(2H, q, J=6.9Hz), 1.27(3H, t, J=6.9Hz), 1.13(3H, t, J=6.9Hz)

Reference Example 162

(E)-8-(2-Bromo-4,5-methylenedioxystyryl)-1,3-diethylxanthine (Compound 165)

Substantially the same procedure as in Reference Example 70 was repeated using 2.50 g (12.6 mmol) of 5,6-diamino-1,3-diethyluracil and 3.77 g (13.9 mmol) of 2-bromo-4,5-methylenedioxycinnamic acid. Then, the resultant crude crystals were recrystallized from dimethylsulfoxide/water to give 2.01 g (yield 38%) of Compound 165 as a yellow powder.

Melting Point: >270 °C

Elemental Analysis: $C_{18}H_{17}BrN_4O_4 \cdot 0.25H_2O$			
Calcd. (%):	C, 49.39;	H, 4.03;	N, 12.80
Found (%):	C, 49.42;	H, 3.75;	N, 12.67

IR (KBr) ν_{max} (cm^{-1}): 1691, 1651, 1497

NMR (270MHz; DMSO-d_6) δ (ppm): 7.78(1H, d, J=8.2Hz), 7.48(1H, s), 7.30(1H, s), 6.97(1H, d, J=8.2Hz), 6.13(2H, s), 4.05(2H, q, J=6.9Hz), 3.93(2H, q, J=6.9Hz), 1.24(3H, t, J=6.9Hz), 1.13(3H, t, J=6.9Hz)

Reference Example 163

(E)-8-(2-Bromo-4,5-methylenedioxystyryl)-1,3-diethyl-7-methylxanthine (Compound 166)

Substantially the same procedure as in Reference Example 1 was repeated using 2.20 g (5.08 mmol) of Compound 165 obtained in Reference Example 162 in place of Compound B. Then, the resultant crude crystals were recrystallized from toluene/cyclohexane to give 1.17 g (yield 52%) of Compound 166 as a pale yellow powder.

Melting Point: 255.1-256.0 °C

Elemental Analysis: $C_{19}H_{19}BrN_4O_4$			
Calcd. (%):	C, 51.02;	H, 4.28;	N, 12.53
Found (%):	C, 50.94;	H, 4.15;	N, 12.39

IR (KBr) ν_{max} (cm^{-1}): 1693, 1651

NMR (270MHz; DMSO-d_6) δ (ppm): 7.87(1H, d, J=15.8Hz), 7.77(1H, s), 7.30(1H, d, J=15.8Hz), 7.32-(1H, s), 6.15(2H, s), 4.10-4.03(2H, m), 4.03(3H, s), 3.92 (2H, q, J=6.8Hz), 1.26(3H, t, J=7.2Hz), 1.13(3H, t, J=6.8Hz)

Reference Example 164

(E)-1,3-Diethyl-8-(2-fluorostyryl)xanthine (Compound 167)

Substantially the same procedure as in Reference Example 70 was repeated using 2.70 g (13.6 mmol) of 5,6-diamino-1,3-diethyluracil and 2.49 g (15.0 mmol) of 2-fluorocinnamic acid. Then, the resultant crude crystals were recrystallized from dioxane/water to give 1.81 g (yield 41%) of Compound 167 as a white powder.

Melting Point: >270 °C

Elemental Analysis: $C_{17}H_{17}FN_4O_2$			
Calcd. (%):	C, 62.19;	H, 5.22;	N, 17.06
Found (%):	C, 62.31;	H, 5.23;	N, 17.09

IR (KBr) ν_{max} (cm^{-1}): 1687, 1650, 1557, 1498, 1451

NMR (270MHz; DMSO-d_6) δ (ppm): 7.81(1H, t, J=7.9Hz), 7.72(1H, d, J=16.3Hz), 7.42-7.25(3H, m), 7.15(1H, d, J=16.3Hz), 4.07(2H, q, J=6.9Hz), 3.94(2H, q, J=6.9Hz), 1.26(3H, t, J=6.9Hz), 1.14(3H, t, J=6.9Hz)

Reference Example 165

(E)-1,3-Diethyl-8-(2-fluorostyryl)-7-methylxanthine (Compound 168)

Substantially the same procedure as in Reference Example 1 was repeated using 1.30 g (3.96 mmol) of Compound 167 obtained in Reference Example 164 in place of Compound B. Then, the resultant crude crystals were recrystallized from toluene/cyclohexane to give 440 mg (yield 32%) of Compound 168 as white needles.

Melting Point: 184.1-184.6 °C

Elemental Analysis: $C_{18}H_{19}FN_4O_2$			
Calcd. (%):	C, 63.15;	H, 5.59;	N, 16.36
Found (%):	C, 63.01;	H, 5.61;	N, 16.27

IR (KBr) ν_{max} (cm^{-1}): 1697, 1668, 1541

NMR (270MHz; DMSO-d_6) δ (ppm): 8.04(1H, t, J=8.4Hz), 7.77(1H, d, J=15.8Hz), 7.47-7.43(1H, m), 7.45(1H, d, J=15.8Hz), 7.35-7.27(2H, m), 4.11-4.04(2H, m), 4.04-(3H, s), 3.92(2H, q, J=7.0Hz), 1.26(3H, t, J=6.9Hz), 1.13(3H, t, J=7.0Hz)

Reference Example 166

(E)-8-[4-(N,N-Dimethylamino)styryl]-1,3-diethylxanthine(Compound 169)

Substantially the same procedure as in Reference Example 70 was repeated using 3.00 g (15.1 mmol) of 5,6-diamino-1,3-diethyluracil and 3.30 g (17.3 mmol) of 4-(N,N-dimethylamino)cinnamic acid. Then, the resultant crude crystals were recrystallized from dioxane to give 2.78 g (yield 52%) of Compound 169 as yellow needles.

Melting Point: >300 • C

Elemental Analysis: $C_{19}H_{23}N_5O_2$			
Calcd. (%):	C, 64.57;	H, 6.56;	N, 19.82
Found (%):	C, 64.78;	H, 6.73;	N, 19.94

IR (KBr) ν_{max} (cm^{-1}): 1691, 1650, 1606, 1530

NMR (270MHz; DMSO-d_6) δ (ppm): 13.20(1H, brs), 7.54 (1H, d, J=16.2Hz), 7.44(2H, d, J=8.6Hz), 6.75(1H, d, J=16.2Hz), 6.74(2H, d, J=8.6Hz), 4.06(2H, q, J=6.9Hz), 3.94(2H, q, J=6.9Hz), 2.97(6H, s), 1.26 (3H, t, J=6.9Hz), 1.14(3H, t, J=6.9Hz)

Reference Example 167

(E)-1,3-Diethyl-8-(4-phenylstyryl)xanthine (Compound 170)

Substantially the same procedure as in Reference Example 70 was repeated using 2.50 g (12.6 mmol) of 5,6-diamino-1,3-diethyluracil and 3.12 g (13.9 mmol) of 4-phenylcinnamic acid. Then, the resultant crude crystals were recrystallized from dioxane/water to give 1.90 g (yield 39%) of Compound 170 as yellow flocculent precipitates.

Melting Point: >270 • C

Elemental Analysis: $C_{23}H_{22}N_4O_2 \cdot 0.25H_2O$			
Calcd. (%):	C, 70.66;	H, 5.80;	N, 14.33
Found (%):	C, 70.90;	H, 5.75;	N, 14.32

IR (KBr) ν_{max} (cm^{-1}): 1689, 1639, 1492

NMR (270MHz; DMSO-d_6) δ (ppm): 7.80-7.65(7H, m), 7.49 (2H, t, J=7.3Hz), 7.39(1H, t, J=7.3Hz), 7.10(1H, d, J=16.3Hz), 4.07(2H, q, J=7.1Hz), 3.94(2H, q, J=6.8Hz), 1.27(3H, t, J=7.1Hz), 1.14(3H, t, J=6.8Hz)

Reference Example 168

(E)-1,3-Diethyl-7-methyl-8-(4-phenylstyryl)xanthine (Compound 171)

Compound 170 (1.50 g, 3.89 mmol) obtained in Reference Example 167 was suspended in a mixed solvent of 13 ml of water, 3.9 ml of a 2N aqueous solution of sodium hydroxide, and 7 ml of methanol. To the suspension was dropwise added 0.55 ml (5.83 mmol) of dimethyl sulfate, and the resultant mixture was stirred at 60 °C for 4 hours. Water (10 ml) was added thereto, and the deposited crystals were collected by filtration and dried. The obtained crude crystals were purified by silica gel column chromatography, followed by recrystallization from ethyl acetate to give 480 mg (yield 28%) of Compound 171 as yellow columns.

Melting Point: 200.5-201.3 °C

Elemental Analysis: $C_{24}H_{24}N_4O_2 \cdot 0.5CH_3CO_2C_2H_5$			
Calcd. (%):	C, 70.25;	H, 6.35;	N, 12.72
Found (%):	C, 70.36;	H, 6.47;	N, 12.60

IR (KBr) ν_{max} (cm^{-1}): 1685, 1649, 1541

NMR (270MHz; DMSO-d_6) δ (ppm): 7.95(1H, d, J=14.8Hz), 7.76-7.69(6H, m), 7.52-7.45(3H, m), 7.39-(1H, t, J=6.4Hz), 4.12-3.99(2H, m), 4.06(3H, s), 3.92(2H, q, J=6.9Hz), 1.27(3H, t, J=6.9Hz), 1.14(3H, t, J=7.0Hz)

Reference Example 169

(E)-1,3-Diethyl-8-(3-fluoro-4-methoxystyryl)xanthine (Compound 172)

Substantially the same procedure as in Reference Example 70 was repeated using 2.50 g (12.6 mmol) of 5,6-diamino-1,3-diethyluracil and 2.72 g (13.9 mmol) of 3-fluoro-4-methoxycinnamic acid. Then, the resultant crude crystals were recrystallized from dioxane/water to give 1.97 g (yield 44%) of Compound 172 as pale yellow flocculent precipitates.

Melting Point: >270 °C

Elemental Analysis: $C_{18}H_{19}FN_4O_3$			
Calcd. (%):	C, 60.33;	H, 5.34;	N, 15.63
Found (%):	C, 59.99;	H, 5.34;	N, 15.57

IR (KBr) ν_{max} (cm^{-1}): 1694, 1644, 1520, 1491

NMR (270MHz; DMSO-d_6) δ (ppm): 7.61-7.54(2H, m), 7.40 (1H, d, J=8.8Hz), 7.21(1H, t, J=8.8Hz), 6.93(1H, d, J=16.3Hz), 4.06(2H, q, J=7.1Hz), 3.97-3.88(2H, m), 3.88(3H, s), 1.25(3H, t, J=7.2Hz), 1.14(3H, t, J=7.1Hz)

Reference Example 170

(E)-1,3-Diethyl-8-(3-fluoro-4-methoxystyryl)-7-methylxanthine (Compound 173)

Substantially the same procedure as in Reference Example 1 was repeated using 1.50 g (4.19 mmol) of Compound 172 obtained in Reference Example 169 in place of Compound B. Then, the resultant crude crystals were recrystallized from toluene/ethanol to give 1.22 g (yield 78%) of Compound 173 as a pale yellow powder.

Melting Point: 211.7-212.2 °C

Elemental Analysis: $C_{19}H_{21}FN_4O_3 \cdot 0.25H_2O$			
Calcd. (%):	C, 60.55;	H, 5.75;	N, 14.87
Found (%):	C, 60.75;	H, 5.81;	N, 14.92

IR (KBr) ν_{max} (cm^{-1}): 1694, 1653, 1544, 1520, 1459

NMR (270MHz; DMSO-d_6) δ (ppm): 7.82(1H, dd, J=12.9, 2.0Hz), 7.59(1H, d, J=15.8Hz), 7.56-7.52-(1H, m), 7.26(1H, d, J=15.8Hz), 7.19(1H, t, J=8.9Hz), 4.10-4.02-(2H, m), 4.02(3H, s), 3.94-3.88(2H, m), 3.88 (3H, s), 1.25(3H, t, J=6.9Hz), 1.13(3H, t, J=6.9Hz)

Reference Example 171

(E)-1,3-Diethyl-8-(4-methoxy-3-methylstyryl)xanthine (Compound 174)

Substantially the same procedure as in Reference Example 70 was repeated using 2.50 g (12.6 mmol) of 5,6-diamino-1,3-diethyluracil and 3.00 g (13.9 mmol) of 4-methoxy-3-methylcinnamic acid. Then, the resultant crude crystals were recrystallized from dimethylsulfoxide/water to give 1.70 g (yield 36%) of Compound 174 as white flocculent precipitates.

Melting Point: >270 • C

Elemental Analysis: $C_{19}H_{22}N_4O_3$			
Calcd. (%):	C, 64.39;	H, 6.23;	N, 15.81
Found (%):	C, 64.05;	H, 6.34;	N, 15.74

IR (KBr) ν_{max} (cm^{-1}): 1689, 1644, 1510, 1459

NMR (270MHz; DMSO-d_6) δ (ppm): 7.56(1H, d, J=16.3Hz), 7.45(1H, s), 7.44(1H, d, J=8.2Hz), 6.98-(1H, d, J=8.2Hz), 6.87(1H, d, J=16.3Hz), 4.06(2H, q, J=7.1Hz), 3.93(2H, q, J=7.0Hz), 3.82(3H, s), 2.18 (3H, s), 1.25(3H, t, J=7.1Hz), 1.13(3H, t, J=7.0Hz)

Reference Example 172

(E)-1,3-Diethyl-8-(4-methoxy-3-methylstyryl)-7-methylxanthine (Compound 175)

Substantially the same procedure as in Reference Example 1 was repeated using 1.27 g (3.36 mmol) of Compound 174 obtained in Reference Example 171 in place of Compound B. Then, the resultant crude crystals were recrystallized from toluene/cyclohexane to give 1.01 g (yield 82%) of Compound 175 as yellow needles.

Melting Point: 176.5-177.6 • C

Elemental Analysis: $C_{20}H_{24}N_4O_3$			
Calcd. (%):	C, 65.20;	H, 6.57;	N, 15.21
Found (%):	C, 65.22;	H, 6.75;	N, 15.22

IR (KBr) ν_{max} (cm^{-1}): 1687, 1648, 1542, 1505, 1434

NMR (270MHz; DMSO-d_6) δ (ppm) : 7.65(1H, s), 7.58(1H, d, J=15.8Hz), 7.57-7.53(1H, m), 7.16(1H, d, J=15.8Hz), 6.97(1H, d, J=8.9Hz), 4.10-4.01(2H, m), 4.01(3H, s), 3.91(2H, q, J=6.9Hz), 3.88(3H, s), 2.19(3H, s), 1.25(3H, t, J=6.9Hz), 1.12(3H, t, J=6.9Hz)

Reference Example 173

(E)-8-(3-Chloro-4-fluorostyryl)-1,3-diethylxanthine (Compound 176)

Substantially the same procedure as in Reference Example 70 was repeated using 2.50 g (12.6 mmol) of 5,6-diamino-1,3-diethyluracil and 3.01 g (15.1 mmol) of 3-chloro-4-fluorocinnamic acid. Then, the resultant crude crystals were recrystallized from tetrahydrofuran/water to give 560 mg (yield 32%) of Compound 176 as a white powder.

Melting Point: >270 °C

Elemental Analysis: $C_{17}H_{16}ClFN_4O_2$			
Calcd. (%):	C, 56.28;	H, 4.45;	N, 15.44
Found (%):	C, 56.30;	H, 4.43;	N, 15.53

IR (KBr) ν_{max} (cm^{-1}): 1695, 1649, 1504

NMR (270MHz; DMSO-d_6) δ (ppm): 7.93-7.91(1H, m), 7.66-7.63(1H, m), 7.58(1H, d, J=16.3Hz), 7.46-(1H, t, J =8.9Hz), 7.08(1H, d, J=16.3Hz), 4.05(2H, q, J=7.1Hz), 3.93(2H, q, J=6.8Hz), 1.26(3H, t, J=7.1Hz), 1.14(3H, t, J=6.8Hz)

Reference Example 174

(E)-8-(3-Chloro-4-fluorostyryl)-1,3-diethyl-7-methylxanthine (Compound 177)

Substantially the same procedure as in Reference Example 1 was repeated using 1.80 g (4.98 mmol) of Compound 176 obtained in Reference Example 173 in place of Compound B. Then, the resultant crude crystals were recrystallized from ethyl acetate to give 820 mg (yield 44%) of Compound 177 as yellow needles.

Melting Point: 218.4-219.1 °C

Elemental Analysis: $C_{18}H_{18}ClFN_4O_2$			
Calcd. (%):	C, 57.37;	H, 4.81;	N, 14.87
Found (%) :	C, 57.23;	H, 4.85;	N, 14.81

IR (KBr) ν_{max} (cm^{-1}): 1693, 1648, 1541, 1505, 1438

NMR (270MHz; DMSO-d_6) δ (ppm): 8.18(1H, dd, J=7.2, 2.3Hz), 7.84-7.79(1H, m), 7.63(1H, d, J=15.8Hz), 7.51-7.44 (2H, m), 4.11-3.99(2H, m), 4.05(3H, s), 3.92(2H, q, J=6.9Hz), 1.25(3H, t, J=6.9Hz), 1.13 (3H, t, J=6.9Hz)

Reference Example 175

(E)-1,3-Diethyl-8-(3-methoxy-4,5-methylenedioxystyryl)xanthine (Compound 178)

Substantially the same procedure as in Reference Example 70 was repeated using 2.50 g (12.6 mmol) of 5,6-diamino-1,3-diethyluracil and 3.31 g (14.9 mmol) of 3-methoxy-4,5-methylenedioxycinnamic acid. Then, the resultant crude crystals were recrystallized from tetrahydrofuran/water to give 600 mg (yield 53%) of Compound 178 as a white powder.

Melting Point: >270 °C

Elemental Analysis: $C_{19}H_{20}N_4O_5$			
Calcd. (%):	C, 59.37;	H, 5.24;	N, 14.58
Found (%):	C, 59.41;	H, 5.26;	N, 14.66

IR (KBr) ν_{max} (cm^{-1}): 1689, 1654, 1640, 1506

NMR (270MHz; DMSO-d_6) δ (ppm): 7.54(1H, d, J = 16.6Hz), 6.94 (2H, s), 6.93(1H, d, J = 16.6Hz), 6.04-(2H, s), 4.05(2H, q, J = 6.9Hz), 3.97-3.88(2H, m), 3.88(3H, s), 1.25-(3H, t, J = 7.2Hz), 1.13(3H, t, J = 7.2Hz)

Reference Example 176

(E)-1,3-Diethyl-8-(3-methoxy-4,5-methylenedioxystyryl)-7-methylxanthine (Compound 179)

Substantially the same procedure as in Reference Example 1 was repeated using 2.00 g (5.20 mmol) of Compound 178 obtained in Reference Example 175 in place of Compound B. Then, the resultant crude crystals were recrystallized from 2-propanol to give 730 mg (yield 35%) of Compound 179 as a yellow powder.

Melting Point: 201.5-202.3 • C

Elemental Analysis: $C_{20}H_{22}N_4O_5$			
Calcd. (%):	C, 60.29;	H, 5.57;	N, 14.06
Found (%):	C, 60.18;	H, 5.72;	N, 13.98

IR (KBr) ν_{max} (cm^{-1}): 1694, 1650, 1543, 1512, 1433

NMR (270MHz; DMSO-d_6) δ (ppm): 7.58(1H, d, J = 15.8Hz), 7.23(1H, d, J = 15.8Hz), 7.20(1H, d, J = 1.0Hz), 7.09 (1H, d, J = 1.0Hz), 6.05(2H, s), 4.09-4.02(2H, m), 4.02(3H, s), 3.94-3.89(2H, m), 3.89(3H, s), 1.25 (3H, t, J = 7.2Hz), 1.13(3H, t, J = 6.9Hz)

Reference Example 177

(E)-1,3-Diethyl-8-(3-fluoro-2-methylstyryl)xanthine (Compound 180)

Substantially the same procedure as in Reference Example 70 was repeated using 2.50 g (12.6 mmol) of 5,6-diamino-1,3-diethyluracil and 2.50 g (13.9 mmol) of 3-fluoro-2-methylcinnamic acid. Then, the resultant crude crystals were recrystallized from dioxane to give 2.18 g (yield 51%) of Compound 180 as a white powder.

Melting Point: >270 • C

Elemental Analysis: $C_{18}H_{19}FN_4O_2$			
Calcd. (%):	C, 63.15;	H, 5.59;	N, 16.36
Found (%):	C, 62.81;	H, 5.71;	N, 16.09

IR (KBr) ν_{max} (cm^{-1}): 1696, 1658, 1499

NMR (270MHz; DMSO-d_6) δ (ppm): 13.7(1H, brs), 7.87(1H, d, J = 16.6Hz), 7.59(1H, d, J = 7.4Hz), 7.31-7.23(1H, m), 7.15(1H, t, J = 8.7Hz), 7.05(1H, d, J = 16.6Hz), 4.06-(2H, q, J = 6.9Hz), 3.94(2H, q, J = 6.9Hz), 2.33 (3H, d, J = 2.0Hz), 1.26(3H, t, J = 7.1Hz), 1.14(3H, t, J = 6.9Hz)

Reference Example 178

(E)-1,3-Diethy1-8-(3-fluoro-2-methylstyryl)-7-methylxanthine (Compound 181)

Substantially the same procedure as in Reference Example 1 was repeated using 1.30 g (3.80 mmol) of Compound 180 obtained in Reference Example 177 in place of Compound B. Then, the resultant crude crystals were recrystallized from 2-propanol/water to give 1.12 g (yield 83%) of Compound 181 as white flocculent precipitates.

Melting Point: 198.1-198.7 • C

Elemental Analysis: $C_{19}H_{21}FN_4O_2 \cdot 0.5H_2O$			
Calcd. (%):	C, 62.45;	H, 6.07;	N, 15.33
Found (%):	C, 62.39;	H, 6.26;	N, 15.25

IR (KBr) ν_{max} (cm^{-1}): 1695, 1654, 1543

NMR (270MHz; DMSO-d_6) δ (ppm): 7.85(1H, d, J = 15.5Hz), 7.75(1H, d, J = 7.9Hz), 7.34-7.27(1H, m), 7.29(1H, d, J = 15.5Hz), 7.18(1H, t, J = 8.9Hz), 4.12-4.04(2H, m), 4.04(3H, s), 3.92(2H, q, J = 6.9Hz), 2.32(3H, d, J = 1.7Hz), 1.27-(3H, t, J = 7.1Hz), 1.13(3H, t, J = 6.9Hz)

Reference Example 179

(E)-8-(3,4-Dihydroxystyryl)-1,3-diethyl-7-methylxanthine (Compound 182)

Compound 74 (2.00 g, 5.20 mmol) obtained in Reference Example 71 was dissolved in 40 ml of methylene chloride. To the solution was added 26 ml (26 mmol) of boron tribromide (1.0M methylene chloride solution) under ice cooling in argon atmosphere, and the mixture was stirred overnight at room temperature. Methanol was added thereto and the mixture was separated with chloroform-an aqueous solution of sodium bicarbonate. The organic layer was washed with a saturated aqueous solution of sodium chloride and dried over anhydrous sodium sulfate, followed by evaporation under reduced pressure. The residue was recrystallized from ethanol to give 643 mg (yield 35%) of Compound 182 as pale yellow grains.

Melting Point: 247.5-248.2 • C

MS-EI m/e: 356(M^+)

IR (KBr) ν_{max} (cm^{-1}): 1675, 1642, 1543, 1520, 1298

NMR (270MHz; DMSO-d_6) δ (ppm): 9.31(1H, brs), 8.95(1H, brs), 7.50(1H, d, J = 15.8Hz), 7.16(1H, s), 7.05(1H, d, J = 7.9Hz), 7.00(1H, d, J = 15.8Hz), 6.77(1H, d, J = 7.9Hz), 4.06(2H, q, J = 6.9Hz), 3.99(3H, s), 3.92 (2H, q, J = 6.9Hz), 1.25(3H, t, J = 6.9Hz), 1.13(3H, t, J = 6.9Hz)

Reference Example 180

(E)-1,3-Diethyl-8-(3-hydroxy-4-methoxystyryl)-7-methylxanthine (Compound 183)

Substantially the same procedure as in Reference Example 61 was repeated using 400 mg (1.12 mmol) of Compound 182 obtained in Reference Example 179 to give 127 mg (yield 76%) of Compound 183 as a pale brown powder. The obtained crude crystals were further recrystallized from ethanol.

Melting Point: 204.5-205.8 • C

MS-EI m/e: 370(M^+)

IR (KBr) ν_{max} (cm^{-1}): 1689, 1653, 1515, 1442

NMR (270MHz; DMSO-d_6) δ (ppm): 9.06(1H, s), 7.53(1H, d, J = 15.5Hz), 7.23(1H, s), 7.17(1H, d, J = 8.3Hz), 7.08(1H, d, J = 15.5Hz), 6.96(1H, d, J = 8.3Hz), 4.06 (2H, q, J = 6.9Hz), 4.00(3H, s), 3.92(2H, q, J = 6.9Hz), 3.82(3H, s), 1.25(3H, t, J = 6.9Hz), 1.13 (3H, t, J = 6.9Hz)

Reference Example 181

(E)-1,3-Diethyl-8-(4-hydroxystyryl)-7-methylxanthine (Compound 184)

Compound 146 (2.70 g, 7.02 mmol) obtained in Reference Example 143 was dissolved in 50 ml of tetrahydrofuran. To the solution was added 17.6 ml of 2N hydrochloric acid, and the mixture was heated under reflux for 2.5 hours. The reaction solution was neutralized with a 2N aqueous solution of sodium hydroxide under ice cooling, water was added thereto, and the deposited crystals were collected by filtration. The obtained crude crystals were recrystallized from 2-propanol to give 2.33 g (yield 98%) of Compound 184 as yellow grains.

Melting Point: >270 °C

Elemental Analysis: $C_{18}H_{20}N_4O_3$			
Calcd. (%):	C, 63.52;	H, 5.92;	N, 16.46
Found (%):	C, 63.17;	H, 6.02;	N, 16.18

IR (KBr) ν_{max} (cm^{-1}): 1696, 1636, 1607, 1517

NMR (270MHz; DMSO-d_6) δ (ppm): 9.79(1H, s), 7.62(2H, d, J=8.3Hz), 7.58(1H, d, J=15.8Hz), 7.08-(1H, d, J=15.8Hz), 6.81(2H, d, J=8.3Hz), 4.07(2H, q, J=6.9Hz), 3.99(3H, s), 3.92 (2H, q, J=6.9Hz), 1.26 (3H, t, J=6.9Hz), 1.13-(3H, t, J=6.9Hz)

Reference Example 182

(E)-8-(4-Benzyloxystyryl)-1,3-diethyl-7-methylxanthine (Compound 185)

Compound 184 (100 mg, 0.29 mmol) obtained in Reference Example 181 was dissolved in 2 ml of dimethylformamide. To the solution were added 162 mg (1.17 mmol) of potassium carbonate and 0.28 ml (2.35 mmol) of benzyl bromide, and the mixture was stirred at 80 °C for 2.5 hours. Water was added thereto under ice cooling to dissolve potassium carbonate and the deposited crystals were collected by filtration. The collected crude crystals were dissolved in chloroform, washed with a saturated aqueous solution of sodium chloride and dried over anhydrous sodium sulfate, followed by evaporation under reduced pressure. The residue was recrystallized from hexane/ethyl acetate to give 67 mg (yield 53%) of Compound 185 as yellow needles.

Melting Point: 184.7-185.4 °C

Elemental Analysis: $C_{25}H_{26}N_4O_3$			
Calcd. (%):	C, 69.75;	H, 6.08;	N, 13.01
Found (%):	C, 69.70;	H, 6.26;	N, 12.79

IR (KBr) ν_{max} (cm^{-1}): 1688, 1655, 1513, 1245

NMR (270MHz; $CDCl_3$) δ (ppm): 7.74(1H, d, J=15.8Hz), 7.53(2H, d, J=8.9Hz), 7.47-7.32(5H, m), 7.01(2H, d, J=8.9Hz), 6.78(1H, d, J=15.8Hz), 5.11(2H, s), 4.21(2H, q, J=6.9Hz), 4.09(2H, q, J=6.9Hz), 4.04 (3H, s), 1.38(3H, t, J=6.9Hz), 1.26(3H, t, J=6.9Hz)

Reference Example 183

(E)-8-[4-(4-Bromobutoxy)styryl]-1,3-diethyl-7-methylxanthine (Compound 186)

Compound 184 (200 mg, 0.59 mmol) obtained in Reference Example 181 was dissolved in 4 ml of dimethylformamide. To the solution were added 163 mg (1.18 mmol) of potassium carbonate and 0.56 ml (1.18 mmol) of 1,4-dibromobutane, and the mixture was stirred at 50 °C for 4 hours. Water was added thereto under ice cooling to dissolve potassium carbonate and the deposited crystals were collected by filtration. The obtained crude crystals were recrystallized from hexane/ethyl acetate to give 170 mg (yield

61%) of Compound 186 as pale yellow grains.
Melting Point: 174.8-176.4 • C

Elemental Analysis: $C_{22}H_{27}BrN_4O_3$			
Calcd. (%):	C, 55.59;	H, 5.72;	N, 11.79
Found (%):	C, 55.68;	H, 5.85;	N, 11.69

IR (KBr) ν_{max} (cm^{-1}): 1688, 1656, 1515, 1244
NMR (270MHz; $CDCl_3$) δ (ppm): 7.74(1H, d, J = 15.8Hz), 7.53(2H, d, J = 8.9Hz), 6.92(2H, d, J = 8.9Hz), 6.77 (1H, d, J = 15.8Hz), 4.21(2H, q, J = 6.9Hz), 4.13-4.02 (4H, m), 4.04(3H, s), 3.50(2H, t, J = 6.6Hz), 2.14-1.93(4H, m), 1.38(3H, t, J = 6.9Hz), 1.26(3H, t, J = 6.9Hz)

Reference Example 184

(E)-8-[4-(4-Azidobutoxy)styryl]-1,3-diethyl-7-methylxanthine (Compound 187)

Compound 186 (235 mg, 0.49 mmol) obtained in Reference Example 183 was dissolved in 10 ml of dimethylformamide. To the solution was added 161 mg (2.48 mmol) of sodium azide, and the mixture was stirred at 80 • C for 3 hours. Water was added thereto under ice cooling and the deposited crystals were collected by filtration. The collected crude crystals were dissolved in chloroform, washed with a saturated aqueous solution of sodium chloride and dried over anhydrous sodium sulfate, followed by evaporation under reduced pressure. The residue was purified by silica gel column chromatography (eluent: chloroform), followed by recrystallization from hexane/ethyl acetate to give 216 mg (yield quant.) of Compound 187 as pale yellow grains.
Melting Point: 158.5-158.9 • C
MS-EI m/e: 437(M^+)

Elemental Analysis: $C_{22}H_{27}N_7O_3$			
Calcd. (%):	C, 60.40;	H, 6.22;	N, 22.41
Found (%):	C, 60.15;	H, 6.31;	N, 22.32

IR (KBr) ν_{max} (cm^{-1}): 2094, 1653, 1605, 1543, 1515
NMR (270MHz; $CDCl_3$) δ (ppm): 7.75(1H, d, J = 15.5Hz), 7.53(2H, d, J = 8.6Hz), 6.92(2H, d, J = 8.6Hz), 6.77 (1H, d, J = 15.5Hz), 4.21(2H, q, J = 6.9Hz), 4.13-3.69 (4H, m), 4.04(3H, s), 3.39(2H, t, J = 6.6Hz), 1.93-1.79(4H, m), 1.38(3H, t, J = 6.9Hz), 1.26(3H, t, J = 6.9Hz)

Reference Example 185

(E)-8-[4-(4-Aminobutoxy)styryl]-1,3-diethyl-7-methylxanthine (Compound 188)

Compound 187 (75 mg, 0.17 mmol) obtained in Reference Example 184 was dissolved in 7.5 ml of tetrahydrofuran. To the solution was added 90 mg (0.34 mmol) of triphenylphosphine, and the mixture was heated under reflux for 3 hours. Water (5 ml) was added thereto and the mixture was heated under reflux for further one hour. After cooling, a 2N aqueous solution of sodium hydroxide was added thereto, and the mixture was extracted with chloroform and dried over anhydrous sodium sulfate, followed by evaporation under reduced pressure. The residue was purified by silica gel column chromatography (eluent: chloroform/methanol/triethylamine) to give 74 mg (yield quant.) of Compound 188. The obtained crude crystals were further recrystallized from 2-propanol/water.
Melting Point: 212.1-214.5 • C
MS-EI m/e: 411(M^+)
IR (KBr) ν_{max} (cm^{-1}): 1692, 1649, 1606, 1544, 1515
NMR (270MHz; DMSO-d_6) δ (ppm): 7.74(2H, d, J = 8.6Hz), 7.62(1H, d, J = 16.2Hz), 7.20(1H, d, J = 16.2Hz), 6.98 (2H, d, J = 8.6Hz), 4.08-3.88(6H, m), 4.02(3H, s),

2.83-2.74(2H, m), 1.82-1.59(4H, m), 1.26(3H, t, J=6.9Hz), 1.13-(3H, t, J=6.9Hz)

Reference Example 186

(E)-8-(4-Ethoxycarbonylmethoxystyryl)-1,3-diethyl-7-methylxanthine (Compound 189)

Compound 184 (300 mg, 0.88 mmol) obtained in Reference Example 181 was dissolved in 10 ml of dimethylformamide. To the solution were added 731 mg (5.29 mmol) of potassium carbonate and 0.47 ml (4.41 mmol) of ethyl chloroacetate, and the mixture was stirred at room temperature for 2 hours. Water was added thereto to dissolve potassium carbonate and the deposited crystals were collected by filtration. The collected crude crystals were dissolved in chloroform, washed with a saturated aqueous solution of sodium chloride and dried over anhydrous sodium sulfate, followed by evaporation under reduced pressure. The residue was recrystallized from hexane/ethyl acetate to give 341 mg (yield 91%) of Compound 189 as pale yellow needles.

Melting Point:	191.8-192.2 °C
MS-EI m/e:	426(M^+)
IR (KBr) ν_{max} (cm^{-1}):	1688, 1658, 1650, 1514, 1440
NMR (270MHz; $CDCl_3$) δ (ppm):	7.74(1H, d, J=15.8Hz), 7.54(2H, d, J=8.6Hz), 6.94(2H, d, J=8.6Hz), 6.79 (1H, d, J=15.8Hz), 4.66(2H, s), 4.29(2H, q, J=6.9Hz), 4.21(2H, q, J=6.9Hz), 4.09(2H, q, J=6.9Hz), 4.04(3H, s), 1.38(3H, t, J=6.9Hz), 1.31 (3H, t, J=6.9Hz), 1.26(3H, t, J=6.9Hz)

Reference Example 187

(E)-8-(4-Carboxymethoxystyryl)-1,3-diethyl-7-methylxanthine (Compound 190)

Compound 189 (200 mg, 0.47 mmol) obtained in Reference Example 186 was dissolved in a mixed solvent of 4 ml of tetrahydrofuran, 4 ml of ethanol, and 2 ml of water. To the solution was added 98 mg (2.34 mmol) of lithium hydroxide monohydrate, and the mixture was stirred at room temperature for one hour. To the reaction solution was added 2N hydrochloric acid, and the mixture was extracted with chloroform and dried over anhydrous sodium sulfate, followed by evaporation under reduced pressure. The residue was purified by silica gel column chromatography (eluent: hloroform/methanol/acetic acid) to give 40 mg (yield 21%) of Compound 190 as a pale yellow solid.

Melting Point:	267.5-269.0 °C
MS-EI m/e:	398(M^+)
IR (KBr) ν_{max} (cm^{-1}) :	1684, 1653, 1647, 1515
NMR (270MHz; DMSO-d_6) δ (ppm):	7.74(2H, d, J=8.6Hz), 7.62(1H, d, J=15.8Hz), 7.20(1H, d, J=15.8Hz), 6.96 (2H, d, J=8.6Hz), 4.70(2H, s), 4.07(2H, q, J=6.9Hz), 4.01(3H, s), 3.92(2H, q, J=6.9Hz), 1.26 (3H, t, J=6.9Hz), 1.13(3H, t, J=6.9Hz)

Reference Example 188

(E)-1,3-Diethyl-8-(3-phenoxystyryl)xanthine (Compound 191)

Substantially the same procedure as in Reference Example 70 was repeated using 3.00 g (15.1 mmol) of 5,6-diamino-1,3-diethyluracil and 4.00 g (16.7 mmol) of 3-phenoxycinnamic acid. Then, the resultant crude crystals were recrystallized from dioxane/water to give 3.82 g (yield 63%) of Compound 191 as pale yellow needles.

Melting Point:	241.4-243.4 °C

Elemental Analysis: $C_{23}H_{22}N_4O_3$			
Calcd. (%):	C, 68.64;	H, 5.51;	N, 13.92
Found (%):	C, 68.26;	H, 5.59;	N, 13.79

IR (KBr) ν_{max} (cm^{-1}): 1640, 1579, 1492, 1265

NMR (270MHz; DMSO-d_6) δ (ppm): 13.52 (1H, brs), 7.87 (1H, d, J=2.0Hz), 7.63(1H, dd, J=8.4, 2.0Hz), 7.56 (1H, d, J=16.3Hz), 7.16(1H, d, J=8.4Hz), 6.95(1H, d, J=16.3Hz), 4.06(2H, q, J=6.9Hz), 3.93(2H, q, J=6.9Hz), 3.89-(3H, s), 1.26(3H, t, J=6.9Hz), 1.14 (3H, t, J=6.9Hz)

Reference Example 189

(E)-1,3-Diethyl-7-methyl-8-(3-phenoxystyryl)xanthine (Compound 192)

Substantially the same procedure as in Reference Example 1 was repeated using 2.00 g (4.97 mmol) of Compound 191 obtained in Reference Example 188 in place of Compound B. Then, the resultant crude crystals were recrystallized from hexane/ethyl acetate to give 1.78 g (yield 86%) of Compound 192 as yellow needles.

Melting Point: 205.1-205.9 °C

Elemental Analysis: $C_{24}H_{24}N_4O_3$			
Calcd. (%):	C, 69.22;	H, 5.81;	N, 13.45
Found (%):	C, 69.02;	H, 5.80;	N, 13.48

IR (KBr) ν_{max} (cm^{-1}): 1692, 1652, 1492, 1241

NMR (270MHz; $CDCl_3$) δ (ppm): 7.74(1H, d, J=15.8Hz), 7.40-6.98(9H, m), 6.88(1H, d, J=15.8Hz), 4.20(2H, q, J=6.9Hz), 4.09(2H, q, J=6.9Hz), 4.04(3H, s), 1.37(3H, t, J=6.9Hz), 1.26(3H, t, J=6.9Hz)

Reference Example 190

(E)-1,3-Diethyl-8-(4-hydroxystyryl)xanthine (Compound 193)

Substantially the same procedure as in Reference Example 181 was repeated using 500 mg (7.02 mmol) of Compound 145 obtained in Reference Example 142. Then, the resultant crude crystals were recrystallized from dioxane/water to give 430 mg (yield 98%) of Compound 193 as pale yellow needles.

Melting Point: >270 °C

Elemental Analysis: $C_{17}H_{18}N_4O_3$			
Calcd. (%):	C, 62.57;	H, 5.56;	N, 17.17
Found (%):	C, 62.60;	H, 5.50;	N, 17.07

IR (KBr) ν_{max} (cm^{-1}): 1674, 1634, 1520, 1488

NMR (270MHz; DMSO-d_6) δ (ppm): 13.34(1H, brs), 9.77 (1H, s), 7.56(1H, d, J=16.2Hz), 7.46(2H, d, J=8.6Hz), 6.81(2H, d, J=8.6Hz), 6.80(1H, d, J=16.2Hz), 4.06-(2H, q, J=6.9Hz), 3.94(2H, q, J=6.9Hz), 1.26(3H, t, J=6.9Hz), 1.14(3H, t, J=6.9Hz)

Reference Example 191

(E)-1,3-Diethyl-8-(4-hydroxy-2,3-dimethylstyryl)-7-methylxanthine (Compound 194)

Substantially the same procedure as in Reference Example 179 was repeated using 500 mg (1.31 mmol) of Compound 82 obtained in Reference Example 79. Then, the resultant crude crystals were

recrystallized from 2-propanol to give 290 mg (yield 60%) of Compound 194 as a pale yellow powder.

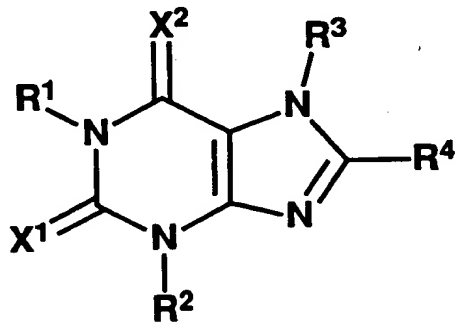
Melting Point:	240.2-242.0 • C
MS-EI m/e:	368(M^+)
IR (KBr) ν_{max} (cm^{-1}):	1683, 1656, 1586, 1460
NMR (270MHz; DMSO-d_6) δ (ppm):	10.20(1H, brs), 9.64 (1H, brs), 7.92(1H, d, J = 15.6Hz), 7.57(1H, d, J = 8.7Hz), 6.97(1H, d, J = 15.6Hz), 6.74(1H, d, J = 8.7Hz), 4.07-(2H, q, J = 6.9Hz), 3.99(3H, s), 3.91 (2H, q, J = 6.9Hz), 2.29(3H, s), 2.10(3H, s), 1.26 (3H, t, J = 6.9Hz), 1.13(3H, t, J = 6.9Hz)

Industrial Applicability

According to the present invention, there can be provided an excellent antidepressant.

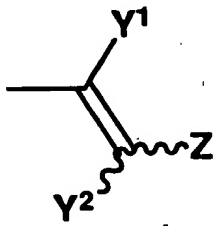
Claims

1. An antidepressant containing as an active ingredient a xanthine derivative or a pharmaceutically acceptable salt thereof, the xanthine derivative being represented by Formula (I):

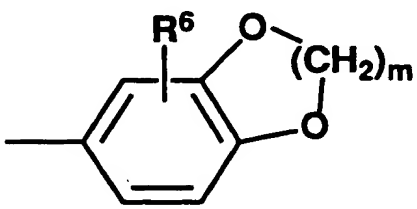


(I)

in which R^1, R^2, and R^3 represent independently hydrogen, lower alkyl, allyl, or propargyl;
R^4 represents cycloalkyl, $-(CH_2)_n-R^5$ (in which R^5 represents substituted or unsubstituted aryl or a substituted or unsubstituted heterocyclic group; and n is an integer of 0 to 4), or



(in which Y^1 and Y^2 represent independently hydrogen, fluorine, or methyl; and Z represents substituted or unsubstituted aryl,



(in which R^6 represents hydrogen, hydroxy, lower alkyl, lower alkoxy, halogen, nitro, or amino; and m represents an integer of 1 to 3), or a substituted or unsubstituted heterocyclic group);
and X^1 and X^2 represent independently O or S.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP93/00931

A. CLASSIFICATION OF SUBJECT MATTER

Int. Cl^5 A61K31/52, C07D473/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Int. Cl^5 A61K31/52, C07D473/06

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	JP, A, 2-56428 (Rohto Pharmceutical Co., Ltd.), February 26, 1990 (26. 02. 90)	1
A	JP, A, 58-109417 (Panmedica S.A.), June 29, 1983 (29. 06. 83), & EP, A1, 74909 & FR, B2, 2531713 & US, A, 4472387	1

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
September 9, 1993 (09. 09. 93)	September 28, 1993 (28. 09. 93)
Name and mailing address of the ISA/ Japanese Patent Office Facsimile No.	Authorized officer Telephone No.

Form PCT/ISA/210 (second sheet) (July 1992)